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U. S. National Institute Health Division
of Research Services.
Report of program activities.

DIVISION

OF

RESEARCH

SERVICES

FY 1978

ANNUAL REPORT

National Institutes of Health
Bethesda, Maryland 20014

U.S. NIH DIVISION OF RESEARCH SERVICES

Report of Program Activities
October 1, 1977, through September 30, 1978

CONTENTS

Page

Office of the Director 1

Biomedical Engineering and Instrumentation Branch 3

Environmental Safety Branch 19

Radiation Safety Branch 29

Library Branch 36

Medical Arts and Photography Branch 40

Veterinary Resources Branch 43

Individual Intramural Project Reports

Biomedical Engineering and Instrumentation Branch

1. The Use of Microprocessor-Based "Intelligent" Machines in Patient Care 63
2. Biophysical Instrumentation and Methodology 65
3. Physical Chemistry of Biological Macromolecules 67
4. Pharmacokinetics 70
5. Implant Device Development 74
6. Trace Element Analysis in Biological Materials 76
7. Particulate Hydrodynamics in Porous Membranes 79
8. Instrumentation for Flow-Through Hollow Fiber Cell Culture Studies 82
9. Flow Visualization Studies in Model Arteries 84
10. Fiber Optic Probes/Oxygen Probes 87
11. Investigation of Oxidative Metabolism and Potassium Kinetics in the Cat Brain 89
12. Two-Dimensional Ultrasonic Imaging System 91
13. Electrical Safety Program for Clinical Center Patients and Patient Care and Treatment Areas 94
14. Development of Whole-Body Hyperthermia Instrumentation and Control System 96
15. Development of an In Vivo Micro Spectrophotofluorometer for Use in Laboratory Animals 98
16. Thermistor Digitizer 101
17. Zeugmatography 103
18. Development of Miniature Catheter for Clinical Use 105

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U56167
1978

Page

19. Fiber Optic Probes/pH Probe 107
20. Multimode Visual Display 109
21. Micropipette Pressure Transducer 111
22. Three-Dimensional Histological Reconstruction 113
23. Counter-Current Chromatography Without Rotating Seals 115
24. Endoscope Introduction 117

Veterinary Resources Branch

1. Animal Model Development 119
2. Development of Diets for Laboratory Animals 121
3. Tyzzer's Disease 123
4. Neoplasia in the Nude Mouse 125
5. Sodium Cyanate Neurotoxicity in Macaca nemastrina Primates . 127
6. Effect of Season on Pituitary and Gonadal Hormone Levels in Adult Male Macaques 129
7. Hormone Levels During the Postpartum Interval in Nursing and Nonnursing Macaques 131
8. Evaluation of Efficacy of M. bovis PPD Tuberculin in the Detection of Tuberculosis in Wild Caught Indian Rhesus Monkeys 133
9. Defining the Nude Mouse Model 135
10. Characterization of a New Viral Disease of Rabbits 136
11. Experimental Atherosclerosis in Miniature Swine 137
12. The Pathogenesis of Chondrodysplasia in the Alaskan Malamute. 139
13. Aging Studies on HSR, HSR-Stroke Prone, and WKY Rats 141
14. Intrautero Injection of Herpes saimiri and Epstein-Barr Virus in Pregnant Guinea Pigs 143
15. Skeletal Age Development in Macaca mulatta 146
16. Anthelmintic Effect on Antibody Levels Following Primary and Secondary Immune Stimulation 149
17. Evaluation of a Purified Diet for Rodents 151
18. Subclinical Ascorbic Acid Deficiency in the Guinea Pig . . . 153
19. Linkage Analysis in the Laboratory Mouse 155
20. Histocompatibility Testing and Blood Grouping of Donor and Inbred Dogs 157
21. Clinical Pathology Studies of Animal Health Conditions . . . 159
22. Evaluation of Mycobacterium paratuberculosis Bacterin in the Goat 161
23. Serum Hormone Levels in Feral Pregnant Rhesus Monkeys . . . 163
24. The Effect of Dietary Crude Fiber on the Digestibility of Proteins, Lipids and Carbohydrates in Macaca mulatta 165
25. Application of Automatic Data Processing to Nonhuman Primate Colony Management 167
26. Reproductive Physiology of Selected Exotic Nonhuman Primates. 169
27. Developmental Parameters of the Foxhound 171
28. Genetic Profile of NIH Inbred Rat Strains 173
29. Fetal Surgery in the Macaca mulatta 175

NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH SERVICES

October 1, 1977, through September 30, 1978

DR. JOE R. HELD, DIRECTOR

The Division of Research Services provides research products and services to intramural scientists and supports extramural activities as well. The Division's programs and activities are known throughout the biomedical research community, nationally as well as internationally. DRS is recognized as a leader in bioengineering and instrumentation, research animal modeling, and environmental health and safety areas. Its support services are considered by NIH scientific and administrative users as essential to continued high performance levels.

User demands and expectations are met with organizational efforts to provide the highest quality product or service economically. This undertaking demands constant analysis and review of the Division's performance areas with a commitment to redesign and restructure, when necessary, to accommodate current and projected biomedical research needs. An important element in addressing changing research priorities is the continued service of the Associate Director for Environmental Health and Safety, the Branch Chiefs, and the Executive Officer. With the Director, they constitute a planning and strategy board for short and long-range programming.

A number of the Division's projects have received special attention by NIH. Progress has been made in the implementation of the National Environmental Policy Act (NEPA) by completing the NIH Generic Analysis. NIH environmental review procedures have been recommended.

Development of a computer system for data on small animals was proposed by DRS. The plan is currently being refined and coordinated with other NIH organizations and the National Center for Toxological Research. Final approval for implementation of the system is expected during FY 1978.

The proposal to purchase acreage adjacent to the NIH Animal Center for current and future research animal production and maintenance facilities has been accepted by the Public Health Service and is under consideration by the DHEW. The Three Springs Farm property, now under long-term lease, is expected to improve the Division's capability to reduce loss of research animals due to disease and infection.

The popular scientific equipment rental program continues to grow in response to user demands. Billing systems are being revised to improve information flow to program managers and the NIH financial community. The rental program provides highly sophisticated, complex instrumentation and equipment to scientists whose hardware needs are temporary and short-term in nature.

Modernization of facilities takes on varying features in an organization as diversified as DRS. Library plans call for expansion of automated systems to complement the recently installed circulation control system As when the circulation system was introduced, professional advice and assistance from the Division of Computer Research and Technology are expected to accelerate implementation schedules.

Building 13 renovation plans will afford the Environmental Safety Branch and Biomedical Engineering and Instrumentation Branch staffs a chance to reprogram to optimize effectiveness. Visibility of environmental health and safety activities and recent additions to bioengineering support functions have increased their space needs beyond current boundaries.

NIH is reviewing the Division's proposal to renovate animal facilities under DRS control. The 14/28 Building Complex will be redesigned to support more research animal holding and experimentation, while reducing animal production in-house to levels dictated by contractors' capabilities and research animal model requirements. Energy conservation measures will be thoroughly reviewed during the planning stages, expected to begin in FY 1979.

Studies related to resource utilization and funding mechanisms are in process. Specific areas under review are the graphics unit of MAPB, glassblowing unit of BEIB, and translation unit of the Library.

Planning and development procedures for Automatic Data Processing systems are being monitored by the Office of the Director. The potential for expansion has already been recognized in radiation safety activities, research animal areas, environmental services functions, and general management information quarters.

Extramural program support was provided through the certification of two P-4 (maximum containment) laboratories for recombinant DNA research. Over forty intramural laboratories were certified for recombinant DNA research; their levels of containment ranged from P-1 to P-3.

The WHO Special Program on Safety Measures in Microbiology was supported through participation in two working group meetings and the development of emergency services for international application.

DIVISION OF RESEARCH SERVICES

BIOMEDICAL ENGINEERING AND INSTRUMENTATION BRANCH

October 1, 1977, through September 30, 1978

DR. MURRAY EDEN, Chief

NIH scientists are becoming increasingly aware of the capabilities of the Biomedical Engineering and Instrumentation Branch with respect to current developments in engineering science, applied physics, and mathematics. As a result, the technical problems presented to BEIB engineers have become more complex and challenging. Meeting the challenge requires broad and intensive collaboration with biological scientists. After converting the demands of the biological problem to technical criteria, we carry the design to practical realization and verify that the technical performance satisfies the biological objectives. Project teams, frequently including several engineering or physical science specialists, are organized to accomplish these tasks.

The range of our projects spans NIH research interests. Most entail design or refinement of instruments to measure, observe, or describe in vitro or in vivo biological systems in an analytic or quantitative way. The systems we have helped to study represent virtually every level of organization: biochemical, cellular, organ or tissue, and holistic.

Novel chemical analytical procedures are being developed or perfected by the Branch. Our facilities for flameless atomic absorption (complemented by neutron activation analyses made by BEIB staff at the National Bureau of Standards nuclear reactor) were used in a study of an important cancer chemotherapy agent, cis-dichlorodiammine platinum (DDP). Pairs of individual optic fibers have been used as the basis for developing an in vivo pH sensor which can be embedded in tissue and is potentially suitable for metabolic studies. The special-purpose colorimeter designed for enzyme-linked immunosorbent assay (ELISA) has already had extensive use in epidemiological studies of a reovirus-like agent implicated in diarrhea of infants.

Much of the work of BEIB is devoted to instrumentation for studies of the physical properties of organs and tissues. Chronically implanted optic fibers were used to measure local perfusion in tumor tissues. Repeating units in a muscle fiber preparation were monitored during contraction by observing a laser diffraction pattern with an electro-optic charge-coupled array. A variety of flow visualization techniques are being applied to the study of flow regimes in models of canine arteries as part of a program to confirm the relation between the formation of atherosclerotic plaque and separation or turbulence in the bloodstream within the artery.

Analyses of physiological systems have been carried out both on an experimental level and on a theoretical level. Pharmacokinetics continues to be a major contributor to progress in this area. Mathematical models have been applied to elucidate the role of Kepone transport in the rat and to predict the scale transformation to man and to the phenomenon of resistance to toxic levels of

methotrexate in the Lewis lung tumor. Theoretical studies of phenomena governing passive transport through pores and gap-junction geometries were pursued. A new instrument system for limb plethysmography capable of modulating the arterial transmural pressure should be valuable in contrasting hypertensive and normotensive compliance curves. A study of stress-coupled transport in aterial sections provides insights into possible models of atherosclerotic lesion formation. A constitutive theory for wound healing that relates biochemical properties to systemic biochemical events appears to describe quantitatively the mechanical properties of healing skin in an animal being treated with adriamycin or X rays.

Whereas all sections of BEIB continue to carry out projects of clinical relevance, a new section was established to concentrate on studies particularly oriented to diagnosis or therapy. A new principle is being applied to the development of a noninvasive visualization technique based on the proton magnetic resonance phenomenon. It should have special importance for the visualization of pathological conditions in infants when X radiation is undesirable or inapplicable because of lack of contrast. Efforts to improve ultrasonic visualization and Doppler blood velocity measurements are going forward. An electrode assembly that "floats" on the cortex has been used successfully for many minutes during cranial surgery for epileptic patients to locate and record spiking cells of epileptogenic foci. For the first time, pharmacokinetic calculation has been used to guide the course of cancer chemotherapy. A programmable calculator-based system has functioned successfully in hyperthermia treatment of patients with advanced stages of cancer.

Research support functions of the Technical Services sections continue to increase; in response, two professional engineers--a mechanical design and an electronic specialist--have been added to the staff. Contracting has been expanded further to take care of the major part of routine fabrication, system maintenance and repair. The Scientific Equipment Rental Program has expanded by about 15 percent in the number of rental contracts and 45 percent in equipment utilization rate. Efforts are being made to enlarge the inventory of devices most commonly required by NIH investigators.

PROJECTS AND ACCOMPLISHMENTS

Engineering and Applied Sciences

1. Chemical Engineering Section

The Chemical Engineering Section provides a broad range of integrated theoretical, experimental, design, and consultative services including analysis of physiologic systems and transport phenomena, analytical methodology, biomaterials, and specialized instrumentation.

The section has developed significant new methodology for application of chemical reaction engineering to a variety of pharmacokinetic problems. Its expertise in pharmacokinetic modeling has become a resource integral to the programs and planning of several NIH components. Particular emphasis has been placed on extrapolations from laboratory animals to man in the pharmacokinetics of environmental contaminants and on laboratory and clinical studies of anticancer drugs.

Progress of fundamental importance to pharmacokinetic theory and clinical practice can be reported. (1) Ovarian cancer is being treated by intraperitoneal administration of anticancer drugs guided by our pharmacokinetic calculations. To our knowledge this represents the first example in cancer chemotherapy of a treatment quantitatively designed from basic principles. Preliminary results support our prediction of a significant concentration difference between peritoneal fluid and plasma. (2) Kepone transport across the gut wall of rats has been quantitatively assessed. Size-scaling concepts have been applied to estimate the upper limit to the rate of removal of Kepone from humans by oral ingestion of adsorbents. Species differences in normal clearance rates and distribution appear to follow rational concepts of scale. (3) Transport studies of methotrexate in the Lewis lung tumor in mice have shown that the resistance of the tumor to levels of the drug toxic to the host may be explained on the basis of pharmacokinetic principles. Tumor permeability is only half that of the gastrointestinal tract, while the target enzyme level is about ten times greater in the tumor.

The transport phenomena program is relatively small, but merits emphasis. We have obtained fluid mechanical correlates of atherosclerosis and believe that synthetic membrane technology will have a constructive influence on biomedical research. Therefore, we are carrying out some independent research to develop mathematical models for passive transport through pores and intracellular gap junctions. The studies will strengthen our ability to respond to requirements for instrumentation involving synthetic membranes and may also enhance biological understanding of the phenomena.

Hemodynamic factors have been implicated in the genesis of atherosclerotic plaque. Our previous work measured the wall shear stress distribution in models of canine arteries. Biological evidence suggests that the flow pattern may also play a role in the development of atherosclerosis. Therefore, our recent studies are designed to identify the various flow patterns, such as separation or disturbance, that can exist in arterial models. Flow visualization methods include dye injection and use of hydrogen bubbles and neutrally buoyant microspheres. In addition, velocity profiles will be measured by laser Doppler techniques. Flow patterns will be studied as a function of flow parameters such as Reynolds number, branch flow ratio, and flow pulse frequency. Correlations will be sought between the shear stress and flow pattern data and the incidence of lesions in experimental animals.

Progress has been made on the theoretical aspects of transport of neutral spherical solutes through slit pores with plane parallel boundaries. Slit-like pores appear to be characteristic of endothelial cell junctions. Our previous analysis has been refined by incorporating numerical evaluation of the Ho and Leal integral expressions for the resistance coefficients of first order in the sphere radius to slit-width ratio. Neutral spherical particles in cylindrical pores have also been examined, and the derivation and evaluation have been completed for the correction to the resistance coefficients of second order in the sphere-to-tube radius ratio. These results should lead to an improvement of the dispersion analysis for convective and diffusive transport.

BEIB develops instrumentation and measurement techniques for a variety of laboratory and clinical studies. Major projects include quantification, identification, and characterization of trace metals in biological tissues, instrumentation for high-density tissue culture, and development of implantable sensors for measurements of tissue pH and oxygen levels.

Our facility for analysis of trace metals by flameless atomic absorption is in continual use by our staff and other NIH investigators. We have also worked closely with the National Bureau of Standards to utilize their nuclear reactor facilities and expertise for neutron activation analysis of trace metals in biological specimens. Qualitative speciation of platinum derived from cis-dichlorodiammine platinum (DDP) is of particular interest because of the possible key role of chemical transformation in the pharmacodynamics of this important anticancer drug. Our pharmacokinetic model for DDP postulates transformation involving the loss of at least one chlorine atom. Three major species are obtained on ion exchange fractionation of urine from a patient treated with DDP. One is water elutable, another acid elutable, and a third strongly bound to the resin. The first predominates in urine collected shortly after drug administration. With time, that form diminishes while the acid-elutable type increases and the resin-bound substance starts to appear.

The development of extremely small probes utilizing pairs of optical fibers has opened the possibility of a wide range of extremely small in vivo detectors that depend on color or fluorescent indicators to measure physiological parameters. Two potentials being actively pursued are sensors for pH and oxygen. Both parameters are important in the investigation of oxygen transport to tissue during exercise. Also, oxygen tension and pH provide information about the growth and development of tumors and their regression in response to therapy. The pH sensor has been developed and evaluated in vitro. It exhibits a precision of 0.01 pH units in the range of physiologic interest and has a time constant of 0.7 minutes. It thus appears suitable for a variety of metabolic studies and is ready for in vivo evaluation. Development of an oxygen probe has been impeded by the lack of a suitable reversible color indicator for oxygen. Work is proceeding on the development of an oxygen indicator dye.

Over a number of years, the section has developed competence to meet NIH's requirements in biomaterials. The biomaterials program is used by investigators studying a wide range of problems in laboratory science and clinical medicine. It serves as a vital link between the biological scientist and the industrial and academic components of the materials field. Success has been achieved in several lines of investigation: (1) The further development of a transthoracic pacemaker had been hindered by mechanical problems with the electrodes. It was discovered that tempering of cobalt-chromium alloys at 770° F increased the flexural fatigue resistance while maintaining adequate stiffness for insertion. (2) Right pulmonary arterial heart assist balloon pumps constructed of segmented polyurethane have functioned successfully when implanted in a series of six sheep. (3) Miniaturized balloon catheters less than 1 mm in diameter with a tip for controlled drug delivery have been developed. These can be pulsed through the arterial system by the flowing blood to reach tumors heretofore inaccessible to treatment.

2. Electrical and Electronic Engineering Section

The staff of this section is primarily concerned with making available to the NIH intramural research program the full power of modern electronic technology. Activities include design and construction of new devices, assistance with selection and application of commercially available apparatus, systems analysis, contract management, and consultation and communication with NIH researchers and members of the electrical engineering profession. The scope of work embraces analog and digital circuit design, hardware and software design for microprocessor-based "smart" instruments, transduction, feedback control systems, video and radio frequency circuitry and systems, electro-mechanical and electro-optical systems, and many other fields:

Microprocessor-based instruments under development include:

-- A second-generation oxygen dissociation curve apparatus in which the microprocessor controls the experimental procedure, acquires and processes data, and records the results on an x-y plotter.

-- A data acquisition system for physiological testing, featuring an interactive mode whereby the researcher controls the acquisition program.

-- An accessory for mass spectrometry, providing scan control as a function of ion current, as well as additional data acquistion and handling features.

-- A data handling system for a microcalorimeter with the ability to offset the baseline and correct the slope, deconvolve the data, and calculate heat of reaction and two rate constants.

Our first usage of new charge-coupled imaging devices occurred with application of a linear array to record a muscle laser diffraction pattern as a function of time. Another major effort in the general area of electro-optics involved peripheral blood flow assessment by a laser Doppler technique. The correlation between the Doppler signal and the flow rate was investigated, and the various signal processing techniques were analyzed for suitability of this application.

In the field of nuclear magnetic resonance, work continued on a custom electron-nuclear double resonance system. The aim of a major new initiative is a physiological imaging system for pediatric use, utilizing magnetic fields in place of ionizing radiation or ultrasonic energy.

Work continued on a solid-state digital system for converting real-time ultrasonic sector scan to a standard video signal. Other continuing projects include: ELISA measurements, ancillary data recording for epilepsy monitoring, proton radiography studies, and adsorption spectrophotometry. New projects were undertaken in the areas of Mossbauer spectroscopy and video display systems.

3. Mechanical Engineering Section

The assistance this section provides to NIH research programs most often consists of specialized and unique instrumentation. Support programs include application of engineering and physical disciplines in such areas as optics, heat transfer, fluid flow, mechanics, ultrasonic, and machine design to specific bioresearch problems. The consultative and design services supplied to Institute research programs are of equal importance. In keeping with our intent to examine and develop new techniques and methodologies which may be significant, the section is exploring fluidic logic, single optic fibers for in vivo implantation development, solar lighting, and improved blood pressure measuring techniques based on oscillometry.

A study has been initiated to optimize and standardize a complex laboratory model of the stop-flow calorimetry system previously developed in a piecemeal fashion. The objective is to examine the limits and acceptable range for various subsystems, overall reliability, ease of operation, and the possibilities of redesign for commercial production.

Each month the media preparation facility requires temporary covering or capping of approximately 22,000 culture media containers to maintain sterility between the autoclaving operation and the filling operation. Studies performed by hand have demonstrated the feasibility of using metal foil for this purpose. Mechanical design and experimentation are now in progress, preparatory to semiautomation of the task. Squares of foil will be applied to containers of different sizes in a rapid, uniform, and consistent manner. A companion device will rapidly remove the caps just before the filling operation.

An improved method of removing tips containing radioactive material from microtiter tubes has been developed. In addition to facilitating and speeding the handling of the sample tubes, the new method significantly reduces the exposure of laboratory personnel to radiation emanating from the samples.

A novel type of valve to control minute flow rates is being developed. The device utilizes pressure generated in a magnetic fluid exposed to a permanent magnet to occlude a flexible elastomer flow passage. When the magnetic field is reduced by an electric current in an adjacent coil, pressure is released, allowing a fluid flow from a reservoir. The device has the potential for high reliability, miniaturization, and implantation where controlled administration of small quantities of drugs, such as insulin, is necessary. A patent covering this device was issued in October 1977.

At the present time no simple, indirect methods are available for measuring blood pressure of animals. The primary problem is to place a transducer and maintain it in position while gauging systolic and diastolic levels. Alternative indirect blood pressure measuring techniques for laboratory animals are being evaluated. The technique currently being studied, oscillometry, does not require a transducer at the measurement site. Oscillometry is a method of measuring blood pressure by monitoring oscillations in cuff pressure with a pressure transducer while the cuff is deflated. During deflation from suprasystolic levels, the first increase in oscillation observed

is taken as the systolic value. The diastolic value can be computed by assuming that the maximum oscillation observed is at the mean value of blood pressure.

A special enclosure for visual response and perception testing of patients has been designed. The complete system includes (1) a background projector system utilizing a fish-eye lens to provide a 360° envelope of images; (2) a spot projector which is computer controlled to move an illumination perception grid to any point within the visual field in 10 milliseconds or less; and (3) a servo-driven chair which can be rotated to present different views of the test pattern envelope to the patient. Support structures are rigid and carry the spot projector assembly in synchronism with the patient.

A recently developed cold-stage microscope viewing platform preserves the required temperature stability and, at the same time, provides transmitted light viewing or reflected light viewing on demand. It uses fiber optics and sapphire windows to furnish heatless light to tissue under study while maintaining temperature stability.

A limb plethysmography system is being devised to allow in vivo correlation of arterial blood pressure and arterial compliance in human beings. The system will be capable of modulating arterial transmural pressure. Of immediate interest will be comparison of hypertensive and normotensive compliance curves and study of changes in compliance as a function of arterial pressure.

The design of a solar lighting system using programmed collectors and mirrors has been made in order to provide cheap, natural lighting for animal facilities buildings. Fitted to a windowless building, the device will provide a prototype study system for extended use.

4. Applied Clinical Engineering Section

This section was established during the fiscal year to provide direct and consultative clinical engineering support to clinical and biomedical research projects at NIH. Close collaboration with researchers is emphasized so that available engineering expertise can be brought to bear while research projects are still in their design phases. Activities include design of new equipment and evaluation of commercial biomedical instrumentation used in clinical research. An important responsibility is an electrical safety program for the Clinical Center, which includes the new Ambulatory Care Research Facility currently under construction.

An automated technique has been developed for obtaining the hemoglobin-oxygen equilibrium curve from samples of concentrated hemoglobin solution or whole blood. Oxygen is exchanged bidirectionally across a silicone rubber membrane with the hemoglobin-oxygen equilibrium curve being calculated by a Tektronix 4051 computer from measured pO_2 values taken as a function of time.

Development of an automated system for determining bacteremia by impedance detection is continuing. The system has been extended to a channel capacity of 60 samples and is in routine use.

A major effort is being made in the support of the Clinical Center diagnostic ultrasound program. An integrated system has been developed that includes a video character generator and an infrared sensitive television camera to add data about the patient and scanner position information to a recorded ultrasonic image. This has facilitated interpretation of scans and also relocation of the scanner on successive procedures.

An instrument to rapidly titrate a sample of protein solution while measuring both pH and heat evolution has been devised. Detector time response between 10 and 90 percent is less than 25 milliseconds for both the thermistor and pH electrodes. A sensitivity of 10 microdegrees and .001 pH unit is available. A new differential AC thermistor bridge and differential pH meter were developed for this system.

A study of stress-coupled transport in biological tissues as related to formation of atherosclerotic lesions is in progress. Effects of hydrodynamically induced wall shear stress on the arterial endothelial surface and related changes in wall permeability to macromolecules are under investigation. The work entails improving a reflectometer used in the measurement of dye-tagged albumin.

A whole-body hyperthermia system has been developed for use as an adjuvant mode of therapy for patients with metastatic cancer. The new system employs water-heated hyperthermia blankets and a water-conditioning system under control of a Tektronix 31 programmable calculator. During this fiscal year, patients have been maintained at 41.8 degrees C for up to five hours per treatment and over 500 hours cumulatively.

A study was undertaken in collaboration with the Chemical Engineering Section to investigate the quantitative and qualitative impairment of wound healing by a variety of cancer therapies, including adriamycin and X rays. A constitutive theory for wound healing relating biomechanics to biochemical events is being developed.

5. Florence Agreement

BEIB implements NIH commitments related to the Florence Agreement. Responsibilities include review of applications for duty-free entry of foreign manufactured scientific apparatus desired by domestic nonprofit institutions, assessment of the suitability of the equipment for intended applications, investigation of availability of domestically produced scientific equivalents, recommendations to the U.S. Department of Commerce for approval, disapproval, or resubmission, and providing pertinent technical advice to requesting agencies and the Department of Commerce.

Complete statistics for FY 78 are not yet available, but the total number of applications processed will approximate 500. An entry for the Federal Register has been prepared. This was necessary in order to clarify the responsibilities of the Department of Health, Education, and Welfare and the Department of Commerce.

Ultramicrotomes of foreign manufacture have had little domestic competition for use in advanced research. Now, however, a new domestic product has been marketed which promises to be competitive with the imports. There is little doubt that an adjustment period will ensue, during which applicants for duty-free imports may have to be informed of the alleged capabilities of the new domestic device.

Technical Services

During the last five years the number of jobs processed by Technical Services has remained constant; however, the complexity of many of these jobs has gradually increased, as have the technical skills and average time required for them. To meet these demands, Technical Services has placed a greater dependence on contracting and is spending additional time on staff training and development. A mechanical engineer and an electronics engineer have been hired to develop employee training programs.

1. Instrument Fabrication Section

An increase in the number of contracted jobs has significantly reduced the overtime workload and the job backlog. Assigning a technician full time to contracting has proven more efficient than having the first-level supervisors handle contracted work.

2. Systems Maintenance Section

Two new areas requiring a significant amount of time are (1) development and implementation of preventive maintenance programs leading to certification by the College of American Pathology and (2) development of the necessary skills to repair, install, seal, and leak-test biological contaminant systems.

The section employs a number of part-time students from local colleges to handle routine preventive maintenance and less complex repairs. The students free other employees for more complex work and serve as a pool of potential employees.

The Scientific Equipment Rental Program is rapidly expanding. It is estimated that both the number of pieces of equipment and the dollar value of the pool will more than double in the year and a half between July 1, 1977 and January 1, 1979. The implementation of the automated record-keeping system will enable the present staff to manage the increased workload. Below is a comparison of the FY 77 and FY 78 rental program operation:

	July 1, 1977	July 1, 1978	Percent Increase
Number of pool items	650	800	23%
Dollar value	$850,000	$1,500,000	75%
Number of items on rental (yearly average)	380	535	40%
Utilization rate	58%	68%	17%

3. Supply Unit

Procedures using computerized listings and reports to reduce the number of items out of stock and expedite special procurement items have increased the overall efficiency of the unit.

Selected Technical Advances

A microprocessor-based "smart" instrument for calorimetric enzyme kinetic studies. The microprocessor carries out various filtering, curve fitting, and processing functions to extract the heat of reaction and two rate constants from the raw data.

A study of the applicability of Moire fringe techniques to measurement of the topology of the fundus of the eye as a possible means for early detection of glaucoma. The problem is difficult because of the shallowness of the topology, diffuseness of the fundus, absence of features that could be used in stereo-photogrammetry, and constraints imposed by the ocular system. It was determined that the theoretically attainable depth resolution was the same for the fringe technique or a photogrammetric technique utilizing projected features, but was deficient by a factor of about five to serve the desired purpose.

A device for integrating flow volumes in a computer-controlled water-feed system for rats. The device will monitor drinking water flow continuously.

A system for detecting and analyzing sounds made by rodents in a behavioral study. A parabolic reflector and ultrasonic microphone sense vocalizations from a seclected animal with output to a real-time spectrum analyzer covering 2 to 100 kHz. Spectra are displayed visually and recorded for subsequent computer processing.

A study of the effect of three polyamines (putrescine, spermidine, and spermine) on the equilibria of magnesium with several nucleotides. The polyamines exert significant influence on the growth and development of lower organisms and mammalian cells.

A simple, humane method for eliminating sick and excessively small animals. A small perforated box containing the animals is placed in a 5½ cubic foot dry ice container. The container is divided into two small sections--one section contains dry ice, and the other section accomodates a box of animals. Once inside the container, the animals are asphyxiated in less than one minute as a result of exposure to the carbon dioxide environment.

An automated plugger inserts cotton into culture tubes. The machine features sensors, indicators, and independent controls for each of the five sections. A newly designed set of self-sharpening cutting shears has been installed. It is intended to cut a minimum of 100,000 segments per year before the device will require attention. The most durable part of the machine is expected to be the control logic modules.

A method for evacuating and sealing ampules containing freeze-dried serum in 30 seconds. The instrument consists of motorized rollers, a gas-oxygen torch, and a vacuum system.

A two-axis, high-speed, servo-controlled tilting mirror system for use with an oculomotor testing apparatus. Accelerations of 75,000 RAD/sec^2 through $\pm 45^\circ$ and $\pm 120^\circ$ are possible.

An optical projection system with computer-controlled slide projection and color control. This is a component of a complex display system for study of patients' perception.

An electrophoresis monitor of voltage gradients in a vertical gel unit. The unit has platinum electrodes inserted into the cell to record the time history of the voltage gradients within the gel.

A flow cell for a fluorescence spectrophotometer. The cell, made of relatively inert compounds, was designed to improve the capability of a Baird Atomic Fluorescence Spectrophotometer.

A laboratory timing device to measure plasma clot destruction times in vitro. Twelve independent samples are accommodated.

An eye contact ring of silicone rubber containing an induction coil used in precise recordings of primate eye movements.

A radiation therapy turntable. The patient may sit or stand, steadied by overhead straps or stanchions in the variable speed, reversible turntable while being treated by radiation from a linear accelerator.

For use with the LKB Mass Spectrometer, a microprocessor-based accessory to monitor the sample chamber temperature and add temperature identification markers to the LKB strip chart recorder. The unit also monitors the total ion current from the sample and automatically initiates a mass scan when the current exceeds a selectable threshold or passes through a peak.

A hand-held lixiscope, acronymic for Light Intensifying X-ray Imaging Fluoroscope. Using a battery-powered image intensifier and a radioactive source in place of an X-ray tube, the device permits clinicians to conveniently view real-time intraoral X-ray images during orthodontic procedures. Suitable radiation shielding, collimation, and electromechanical packaging techniques were employed to ensure patient and user safety and minimum downtime.

Training

An effective professional and technical training program helps BEIB maintain a high quality of engineering and technical service support. BEIB employees participated in 187 academic, administrative, and technical courses, including 29 formal university courses taken for credit. Whereas 20 employees received specialized training on scientific equipment from various manufacturers, 88 attended administrative, clerical, technical, and scientific seminars and short courses, and 2 are currently enrolled in Upward Mobility College.

PLANS

The primary responsibility of BEIB is to provide engineering support and technical services to the intramural program of NIH. Specific activities reflect both the needs of NIH and the human and material resources available to the Branch. As these resources are expected to remain severely restricted in the immediate future, the Branch must attempt to optimize their use through closer and continuing interaction with NIH scientists in defining and pursuing those areas of development that are likely to be significant.

It must also coordinate and direct constructive relationships with other goverment agencies, universities, and the private sector. Further, the Branch staff must be alert to opportunities for the development of new technology. It requires an environment in which creativity and initiative are recognized and rewarded.

BEIB plans pertain both to engineering and technical services:

1. Emphasize projects that have known potential for significantly advancing our ability to (a) observe, describe, and analyze biological systems or (b) provide technology to clinical medicine.

2. Encourage initiatives in developing new technology relevant to the mission of the Branch.

3. Develop our staff through in-house training, short courses, advanced study, research, and participation in professional and technical societies.

4. Exploit resources of other government agencies and private companies for contract of routine and production-type work and for required capabilities not available in house.

5. Use outside staff on short-time or slot-free assignments through, for example, the Visting Program, Intergovernmental Personnel Act. Stay-in-School Program, New Careers Progam, and Guest Worker Program.

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DIVISION OF RESEARCH SERVICES

ENVIRONMENTAL SAFETY BRANCH

October 1, 1977, through September 30, 1978

MR. VINSON R. OVIATT, Chief

The year was marked by an increased level of direct Environmental Safety Branch service to the NIH intramural research effort. An outstanding example was the certification of the maximum containment P4 laboratories at the Frederick Cancer Research Center (FCRC) and on the NIH campus. The attendant safety manuals and certification test methods will serve as models for the total biomedical research community.

We continue to stress safe use and disposal of carcinogenic and other hazardous chemicals used in research procedures. The work includes training courses, laboratory surveillance, and development of safe procedures. A contract research project to develop a safe means for the destruction of chemical carcinogens by incineration shows promise.

The many construction projects on the NIH campus brought with them additional safety problems. A construction safety committee was formed to coordinate construction and safety activities. Centralization of the issuance of safety equipment benefited all employees. Now safety glasses, respirators, and other personal protection equipment may be obtained from one Branch office.

Service to the research community beyond NIH was continued. Leadership and professional services were provided the World Health Organization's Working Group on Laboratory Safety Elements. A cooperative program with the National Sanitation Foundation in the development of laboratory safety equipment passed a milestone with the first national certification of laminar flow biological safety cabinets.

A word of appreciation is extended to the many college and university students employed by the Branch during the year. They worked in our laboratories, assisted in laboratory certification and other special projects, and made required safety evaluations of NIH work places. Without their assistance, the professional staff would not have been able to perform the activities listed in this report.

Two Branch staff members received special recognition for their achievements:

Mr. Vinson R. Oviatt - The NIH Director's Award

Dr. Lloyd G. Herman - Man of the Year Award from the Environmental Management Association

PROJECTS AND ACCOMPLISHMENTS

Administration and Environmental Planning

Proposed procedures were drafted for environmental review of NIH projects. These procedures are required by the National Environmental Policy Act (NEPA). As this effort was being completed, the Council on Environmental Quality (CEQ) published proposed regulations for implementing procedural provisions of the Act. The regulations represent a significant change, as previously CEQ only provided guidance to federal agencies.

Biosafety and Contamination Control

The NIH Guidelines for Research Involving Recombinant DNA Molecules (hereinafter, "Guidelines") continued to generate a significant workload for the Branch. Major activities include:

*Twenty-eight Intramural Memoranda of Understanding and Agreement (IMUA's) submitted by NIH investigators were approved by the NIH Biosafety Committee. The approval process is managed by the Committee's Executive Secretary (Chief, ESB). Branch staff surveyed the laboratories where the research will take place and certified that they meet the Guidelines' physical standards.

*Certification procedures were completed for two P4 (high-hazard containment) laboratories. The first NIH P4 facility to be certified (located in Building 550, FCRC) met physical containment requirements in December 1977. approximately one year after remodeling and testing began. Research started in the facility in April 1978 after a laboratory personnel training period and fulfillment of other requirements. The second P4 facility (the Mobile Containment Laboratory) was certified on May 30, 1978. Certification of the physical containment was completed in 18 months. These projects required approximately 1 and 1/2 man-years of Branch staff time.

*Two additional facilities are being renovated to meet the P4 standards in the Guidelines: B-100 Suite, Building 41, and Building 41T. Branch staff are responsible for testing the facilities to determine if they meet standards.

The Branch is responsible for monitoring laboratory safety containment equipment. Five hundred and twenty-two safety cabinets, clean benches and animal isolators were tested under contract to ensure that the equipment was operating as designed. Also included in this contract are testing and repair of building system exhaust filters, vacuum system filters, and sterilizers in biohazardous containment areas and space decontaminations.

ESB continues to support the National Sanitation Foundation (NSF) program for testing Class II biohazard cabinetry. The first listing of approved equipment became effective April 1978. Seventy-three new Class II biological safety cabinets that conform to the NSF standard were purchased and installed. Twelve Class II cabinets were provided to NIH investigators as part of the Branch Emergency Issuance Program.

Before equipment from laboratories working with biohazardous agents can be repaired or released to surplus, it must be cleaned to assure that the agents are completely removed. The Branch operates and maintains a special room for decontaminating equipment that laboratory personnel cannot clean because it is too delicate or too complicated. We decontaminated 130 pieces of equipment during the year for the Division of Administrative Services (Personal Property Branch), Division of Research Services (Biomedical Engineering and Instrumentation Branch), National Cancer Institute, and National Institute of Allergies and Infectious Diseases.

The Branch provides expert advice on the control of hazardous biological agents in the laboratory. NIH investigators requested 154 consultations, and individuals outside NIH requested 45. A consultation normally consists of giving advice on the selection and proper use of equipment, safety devices, and biohazards control and usually requires four hours' staff time.

NIH uses 49 different sizes of High Efficiency Particulate Air (HEPA) filters and needs a comprehensive specification to cover the various sizes. The Branch has entered into an operational interagency agreement with the Chemical Systems Laboratory, U.S. Armament Research and Development Command, DoD, Aberdeen Proving Ground, Maryland, to develop two military specifications, one for HEPA filters and one for HEPA filter medium. The agreement entails development of a Qualified Products List. The military specification now used was developed for the use of the Nuclear Regulatory Commission and covers only five sizes of filters. The project should be completed in March 1979.

Industrial Hygiene

ESB industrial hygienists conducted a wide variety of occupational health evaluations. Toxicity and industrial hygiene recommendations based on these evaluations are made to NIH staff, as well as others both in and outside the government service. Chemical safety data sheets are prepared as required.

An asbestos evaluation, control, and training program was developed. NIH work places where asbestos is known to be present or is suspected are the focus of this program. Branch staff develop control equipment or procedures for NIH employees. A slide/cassette training package was developed for employees who work with or near asbestos.

Two visits were made to the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, in response to management and employee health concerns. The concerns grew out of earlier accidents and exposures combined with the problem of an inadequate laboratory facility. Improving procedures and facilities has alleviated the problems.

The Branch, in conjunction with the Occupational Medicine Service, developed a hearing protection program for NIH employees which includes environmental monitoring, audiometric examinations, engineering recommendations, and specification of personal protective equipment.

We established a central respirator program to provide NIH employees with evaluations of the need for a respirator and advice on respirator selection

and use. A special test booth has been obtained; it is used for showing persons how to fit and use respirators.

NIH has 795 chemical fume hoods located throughout its laboratory facilities. All hoods are inspected annually under contract for malfunctions. When necessary, Branch staff conduct special investigation of the fume hoods.

Odor complaints by NIH employees--116 this year--create a major workload. Although the causes are usually simple, ranging from dry traps in laboratory plumbing to use of an unventilated room for animals, odors in work spaces sometimes indicate loss of control over a chemical potentially harmful to NIH employees.

Safety Management

The objective of the Safety Inspection Program, namely, to inspect all NIH work places, was met this year. Branch safety staff made recommendations to eliminate or reduce a wide range of physical hazards. While this program is generally effective, laboratory users often fail to cooperate fully, typically with regard to storage and handling of chemical stocks and housekeeping practices. One outstanding exception is the Clinical Pathology Department of the Clinical Center. That department, striving to upgrade its safety posture, has developed an enthusiastic safety committee which is preparing a comprehensive safety manual covering its operations. In part, the project evolved from activities of the Clinical Center safety committee, which has played a positive role in developing and encouraging safe procedures.

The staff, working with individual B/I/Ds, has noticed a general increase in the activities of several safety committees. However, some of the Institutes, while they have a safety committee, do not appear to be effectively utilizing them. We have been encouraged by the support and cooperation received from the Division of Engineering Services and the major contractors operating at NIH. Safety programs at the three major construction sites (Ambulatory Care Research Facility, Lister Hill, and Radiation Oncology) are far superior to those seen in previous years.

Publication of safety information on serious accident potentials in the laboratory has created unexpected returns. For example, accident reports describing perchloric acid explosions resulted in a significant number of calls from the scientific community requesting additional information or advice on similar usage at NIH. Increased awareness of the use of perchloric acid at NIH prompted us to examine safe alternatives to the usual hood designed specifically to accommodate perchloric acid work.

NIH accident data are analyzed continually. There is a modest increase in both the number of injuries resulting in the employee being unable to return to work on the day following the accident and the length of such disabilities. However, we have not seen this pattern expressed in the laboratory environment. A portion of the increase must be attributed to the award decisions made by the Department of Labor's Office of Workers' Compensation. We were pleased to see they have taken steps to tighten up and improve their claims procedures toward the end of FY'78. Such steps, coupled with the Compensation

Officer's efforts to improve our internal procedures, are expected to result in a truer "accident picture" during the coming months.

The requirement for high-purity acetylene associated with atomic absorbtion analyzers continues to create problems related to storage of standby cylinders and supply schedules. The staff has started to evaluate simple equipment that would permit the use of commercial grade acetylene with such analytical equipment, while still ensuring the safety of the equipment. The plan, if satisfactory, will materially improve delivery schedules, reduce the need for standby cylinders, and reduce the cost of the acetylene by an estimated 50 percent.

The Branch is participating in a premarket evaluation sponsored by one of NIH's major chemical suppliers. The supplier is testing a chemical container intended to prevent glass container breakage.

A series of "Mini-Safety Data Sheets" were prepared to provide information about commonly used laboratory equipment. Brief, they are intended to highlight principle hazard potentials associated with the use of laboratory equipment.

General Sanitation and Sanitary Engineering

Branch staff contributed to the successful conversion of the NIH solid waste system. The basic change, from handling medical-pathological waste in lined GI cans to a one-way bag and box container system, was completed this year. The new system is acceptable to NIH staff and can be accommodated by our incinerators. Monitoring the system, investigating problems immediately, and training NIH workers will be necessary to ensure that the new system works well. Until this year, all of the training has been on either a written or person-to-person basis. Seeing the need for improved training, ESB has developed and completed under contract a slide/tape presentation aimed at waste producers. The presentation will be set up and shown in each work area.

Disposal of toxic, carcinogenic, or environmentally harmful chemicals from research facilities has become an increasingly serious problem and one that is extremely difficult to solve. Thoughtful scientists and environmentalists recognize that we cannot continue to use special chemical waste landfills to the degree that we do now. Not enough is known about the performance of high-temperature destructors, an attractive alternative as they almost completely destroy organic materials which constitute a major portion of the NIH chemical waste load. To help meet the need, the Branch has issued a contract for evaluating a number of existing chemical destructors. A standard test charge containing several types of chemicals and two tracer chemicals is used to provide a measure of destructor efficiency. Field testing will not be completed until early next fiscal year.

A research project entailing chemical analysis of sediment from the Choptank and Tred Avon Rivers of Maryland for Mirex was conducted at the request of National Marine Fisheries Service, USDA, Oxford, Maryland. Mirex is thought to be the cause of an outbreak of epizootic carcinoma in Macoma balthica

and Mya anevavia clams. Other government agencies such as FDA and EPA collaborated in the project.

The Branch monitored and evaluated NIH facilities to identify animal care sanitation problems and provide appropriate corrective recommendations. Regular surveys were also made of potable and wastewater at NIH and the NIH Animal Center. Water quality of Broad Run at Poolesville, Maryland, is continuously monitored by automatic water analyzers.

ESB is responsible for ensuring the high quality of NIH cafeterias and snack bars. These establishments were semiannually inspected and a special trip was made to the National Institute of Environmental Health Sciences at Research Triangle Park, North Carolina, to inspect their cafeteria.

A comprehensive survey of all drinking fountains on the reservation was started in July. Regular cleaning does not appear to be a routine practice, except in the Clinical Center. Over 75 percent of the fountains have higher than acceptable levels of viable bacteria, including about 10 percent with viable acid-fast contaminants.

Hospital Environmental Control

The Branch continually monitors the NIH Clinical Center environment. Safety and sanitation surveys were made of the 22 nursing units and the following departments: Anesthesiology, Blood Bank, Diagnostic Radiology, Nuclear Medicine, Outpatient, Pharmacy, and Rehabilitation. An environmental survey of the Pharmacy Department indicated that the laminar flow hoods reduced air contamination significantly. A new recovery room, checked for contaminants, has an excellent air supply.

Environmental Studies for Support of Research and Patient Care

A study comparing the effectiveness of a phenolic disinfectant versus a quaternary disinfectant was performed in the Clinical Center. Neither disinfectant was altogether satisfactory for reducing floor contamination, and good cleaning programs still depend on the conscientious efforts of dedicated workers.

A study on a self-contained space suit indicated that excellent control of contaminants through the special fan and filter unit was possible. Modifications to reduce the noise level have resulted in an acceptable unit for leukemia patients who should breathe only sterile air.

Problems with mold contamination are continuing in most high-humidity tissue culture incubators. Spraying with Cunilate compound (a copper base fungicide) at quarterly intervals seems to be the most effective solution.

The National Disaster Evaluation Team requested help in evaluating the flood damage to several hospitals and public buildings in New Orleans. Fortunately, the water supply was not affected, but flood water damaged several areas extensively. The chief problem was mold growth on dry wall areas in buildings and private residences. Stricter control of building permits and basement construction and use would prevent many problems.

The quality of water used by NIH investigators affects their research. The Branch conducted two complete assessments of NIH central distilled water systems for copper content, which is used as an indicator of the systems' general condition and capability to produce high-quality water. We continually survey the market for materials used in high-purity water systems and test them. A new material, TEFZEL, has been selected for the central distilled water system in the new Ambulatory Care Research Facility. The distribution system will serve specific laboratories as opposed to hallway taps.

Media and Glassware Production

Projected workload figures show increased production on both media and glassware services. Total volume of media produced increased 7.7 percent with 156,000 liters issued, and glassware by 5.6 percent with 6,992,000 pieces issued. Significant trends were noted in the number of media requests, which increased over 9 percent, and the number of agar petri dishes issued, which increased 12.5 percent.

The trend of using commercially supplied tissue culture media to supplement in-house production continued this year with 6 percent of the total volume issued being purchased from commercial sources. This figure represents most of the increase in production and is a further indication that the Media Unit has reached the maximum production possible with present manpower and space allocations.

Several pieces of new equipment were added to improve the quality of media and glassware services. Two new glass water stills of the Karamian design were added to perfect water for media production. A new test tube plugging machine designed and fabricated by the Biomedical Engineering and Instrumentation Branch (BEIB) contributed to increased production of a more uniform product. BEIB initiated design and fabrication of a bottle-covering machine to aid production of this high volume item of glassware.

Installation of gold fluorescent lights in the tissue culture media preparation and dispensing areas to replace the white fluorescent lights was a significant contribution to improved quality of media. Reports in the literature of phototoxicity attributed to excessive exposure to white light of tissue culture media led to the improvement.

Renovation in the glassware sorting, inspection, and sterilization areas to provide more pleasant and productive work areas was completed during the year, with a noted improvement in employee morale. Modifications to the air handling and cooling systems throughout the area also had a beneficial effect on employee morale.

Loose rubber liners in media bottle caps supplied by contractors have prevented an air-tight seal. The recurring problem was solved by an employee suggestion involving a change in the method of sterilizing the caps to provide better adhesion of the liner to the inner cap surface.

A management study to determine current and future capabilities and production requirements of the Media Unit was completed, and a number of

recommendations were made regarding automation and space allocation. Implementation of these ideas will proceed within personnel and space limitations.

Training

Three laboratory safety training projects are essentially complete. Two one-day safety training programs, "Hazardous Chemical Safety" and "Fundamentals of Biosafety," are designed to effectively present the material in a normal workday and are complete with related visual and printed material. The third consists of programmed instruction material to serve as a primer for laboratory safety.

In addition, slide-cassette training instruction was supplied to 26 investigators here at NIH and 20 away from NIH. Also, a lecture on biohazards control was given to 150 persons in Cincinnati.

Approximately 275 copies of the NIH Biohazards Safety Guide were distributed to interested individuals outside NIH and 20 to NIH investigators. The publication is being revised to incorporate standards set forth in the NIH Guidelines.

A quarterly memorandum, "Biological Laboratory Hazards," was distributed to more than 250 laboratories, including several overseas institutions. In addition, miscellaneous biohazard control information was sent to over 50 investigators outside NIH.

PLANS

In general, the Branch will continue ongoing programs. Significant changes in Branch production are not expected unless staffing levels increase. Projected directions in program areas are listed below.

Administration and Environmental Planning

Measures taken by the Council on Environmental Quality will initiate a process whereby DHEW, PHS, and NIH will examine existing NEPA policies and procedures. A number of policy documents will be reviewed and issues resolved. The coming year will see changes in existing NEPA programs.

Industrial Hygiene

A new chemical carcinogen questionnaire will be developed to obtain information about NIH's usage of such chemicals; the data will be used for program management in this complex area. In cooperation with the Occupational Medicine Service, CC, a study of the impact of animal dander allergy on the health of workers will be undertaken. It is anticipated that monitoring in the work place will be augmented to document the degree of worker exposure to various substances in the environment.

General Sanitation and Sanitary Engineering

The chemical destructor study will be completed and specific recommendations made to NIH management. Automated water monitoring stations at the NIH

Animal Center will be updated to provide for telemetry of data and improved data handling. Provision may be made for automated sampling and analysis of NIH wastewater released to the Washington Suburban Sanitary Commission sewer system. The chute system in the Clinical Center for solid waste transport will be put into operation.

Biosafety and Contamination Control

Program emphasis will continue to be directed toward meeting NIH researchers' needs concerning IMUA reviews and laboratory physical standard certifications under the NIH Guidelines for Research Involving Recombinant DNA Molecules. Annual recertification of laboratories is also required.

Training

Training programs developed this year will be implemented in the coming months. It is hoped that we will be able to establish techniques to accurately measure the impact such training has on employee awareness and accidents. In this regard, we anticipate utilizing a safety questionnaire. The data collected will serve to better define additional safety training needs.

During the coming year we will try to improve communication of safety information. Included in this effort will be the reestablishment of a quarterly safety publication, examination of alternative means of communicating safety concerns, and the development of additional visual and audiovisual materials.

Safety Management

Shortly after the beginning of the fiscal year, the Safety Office will start issuing safety shoes, now being handled by the Division of Engineering Services. All safety-related equipment will be stocked and issued by the Safety Office. In addition, the recently acquired respirator test booth will be operated by the Safety Office staff.

Media and Glassware Production

Maximum effort will be directed to acquiring and phasing into production automated equipment which will provide increased efficiency in high workload areas. The need for additional automation in container labeling became more pressing with a requirement for labeling each agar plate, tube, and bottle of media with the type of medium and expiration date. This change will meet criteria for accreditation of the Clinical Pathology Department, which was recently inspected by the College of American Pathologists.

The limulus amebocyte lysate assay, a test for endotoxins, will be considered as an addition to our media quality control program. This test, shown to be more sensitive than the USP rabbit test for endotoxins, is based on an enzymatic reaction; endotoxin activation of a high molecular weight enzyme converts a low molecular weight clottable protein to a gel.

The National Cancer Institute's animal rooms in the Clinical Center have been consolidated into the B-1 and B-2 corridors. The resultant

more stringent cagewashing requirements will necessitate a scheduling plan to interface NCI needs with those of other organizations located in the Clinical Center.

Program changes which may become necessary in the coming year because of personnel shortages and space limitations are elimination of one-liter media bottles, serum additions by the Media Unit to prepared media, and contracting of demineralized water production.

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DIVISION OF RESEARCH SERVICES

RADIATION SAFETY BRANCH

October 1, 1977, through September 30, 1978

MR. MICHAEL MUSACHIO, Chief

The National Institutes of Health are authorized to procure and use radioactive materials on the Bethesda reservation under a Type A specific license of broad scope issued by the Radioisotopes Licensing Branch, Division of Materials and Fuel Cycle Facility Licensing, U.S. Nuclear Regulatory Commission (NRC). This license is contingent upon the existence of a Radiation Safety organization. That function is fulfilled by the Radiation Safety Branch (RSB). In size and scope the NIH Radiation Safety Program is one of the largest in the world, being exceeded by only a few of the National Radiation Laboratories operated by the Energy Research and Development Administration.

Some sources of ionizing radiation are not covered by the NRC License. They include X-ray equipment, high-energy particle accelerators, and naturally occurring or accelerator-produced radionuclides. Those sources are, however, controlled by an Executive Order relative to compliance with rules and regulations issued by the Occupational Safety and Health Administration of the U.S. Department of Labor and Food and Drug Administration and NIH policy promulgated upon the recommendation of the Radiation Committee, NIH.

The Radiation Safety Branch, under the direction of the NIH Radiation Safety Officer, is responsible for:

1. General surveillance of all health physics activities, including both personnel and environmental monitoring.

2. Furnishing consulting services to personnel at all levels of responsibility on all aspects of radiation protection.

3. Receiving, delivering, and shipping all radioactive materials coming to or leaving the NIH reservation.

4. Assaying all radioactive materials to be used in human beings for therapeutic purposes.

5. Monitoring all accelerators and other machines capable of producing penetrating radiation. Calibrating the output of the machines as requested.

6. Distribution and processing of personnel monitoring equipment. RSB keeps records of internal and external radiation exposure of personnel, notifies individuals and their supervisors of exposures approaching the maximum permissible amounts, and recommends appropriate remedial action.

7. Instructing personnel in proper procedures for the use of radioactive materials.

8. Supervision and coordination of the waste disposal program, including keeping records of waste storage and disposal.

9. Operation of the Isotope Laboratory, Building 21. This laboratory is equipped for handling high levels of activity not normally permitted in the typical NIH laboratory.

10. Storage of all radioactive materials not in current use.

11. Performing leak tests on all sealed sources.

12. Maintaining an inventory of all radioactive materials on the NIH reservation.

13. Supervising decontamination in cases of accidents.

14. Continuously evaluating and eliminating environmental radiation hazards.

PROJECTS AND ACCOMPLISHMENTS

Licensing

An application was submitted to the NRC for renewal of License 19-00296-10 (Type A Specific License of Broad Scope), which was scheduled to expire on April 30, 1978. This license remains in effect pending action by the NRC on the application.

License SNM-279 was permitted to expire as the result of the National Heart, Lung, and Blood Institute terminating a study to evaluate nuclear-powered cardiac pacemakers implanted in dogs. Thirty pacemakers were transferred to the Argonne National Laboratory, in accordance with regulatory requirements, at the conclusion of the study. The license also permitted the possession and use of two plutonium-beryllium sources for calibration of neutron detection instruments. With its termination, it was necessary to amend License 19-00296-10 to permit the continued use and possession of these neutron sources.

A 3,450-curie cobalt-60 teletherapy source and its depleted uranium shield (License 19-00296-16) were transferred from the Radiation Oncology Branch, NCI, to Neutron Products, Inc., Dickerson, Maryland, in preparation for shipment to the Cancer Institute in Cairo, Egypt. Since the unit was not replaced, the license was terminated. A subsequent inspection by a representative of the NRC indicated that the transfer was accomplished in accord with all applicable regulatory requirements.

An application was submitted to the NRC to amend License 19-00296-17 so as to permit the possession and use of two additional cesium-137 irradiators. If approved, NIH will have a total of five cesium-137 irradiators with a possession limit of 10,400 curies.

A major NRC inspection was conducted relative to licenses 19-00296-10 and 19-00296-17 on April 18-20, 1978. At the same time, an investigation was made of a possible personnel overexposure which was reported earlier to the NRC in accordance with the provisions of 10 CFR 20.403. The investigation indicated that the possible overexposure was due to a contaminated film badge and was not an actual personnel exposure. As a result of the inspection, NRC requested NIH to reexamine: its policy for monitoring the extremities of phosphorous-32 workers, its administrative procedures for assuring radiation safety training to all radiation workers, and its policies to limit access to radioactive materials in unrestricted areas.

The Radiation Safety Branch reviewed over 200 applications for authorization to purchase and use radioactive materials (NIH Form 465-1) and forwarded 182 applications to the Radiation Committee with recommendations for approval. This brings the total number of authorized active users at NIH to 812. In addition, an examination was developed and administered to several applicants who claimed to have had training equivalent to the "Radiological Health for Radionuclide Users" course. RSB also reviewed 76 applications for renewal of radionuclide authorization. These authorizations are valid for 3 years. In addition to updating their training and experience, applicants for reauthorization must attend a "Radiation Safety Review" program presented by RSB.

The Radiation Committee instigated a policy to reevaluate on an annual basis all protocols that exceed the maximum activity permitted for routine laboratory use under NIH guidelines. Of the 51 reviewed, 28 were renewed and 23 retired. Five planned projects were submitted for RSB review before consideration by the Radiation Committee.

Radionuclide Receipt and Delivery

A total of 167,149 millicuries of radioactive materials (excluding nuclear pacemakers) in 13,444 shipments was received during the year. The value of the materials was $2,532,062.

The Radiation Safety Branch also prepared 184 packages of radioactive materials for shipment from NIH investigators to authorized domestic and foreign licensees.

Radioactive Waste Disposal

Radioactive waste pickup, processing, packaging, and disposal activities are conducted under contract. However, under the provisions of NRC License 19-00296-11, NIH bears the ultimate responsibility for the safe and proper handling of licensed radioactive waste until it is transferred to another authorized licensee. That occurs as soon as the contractor takes the waste off the NIH reservation. The contract is working well with radioactive

waste generally being removed from the laboratory within 24 hours after request for pickup. However, a number of difficulties have been encountered in the solicitation of bids and award of this contract on an annual basis. Therefore, an effort is being made to provide NIH with the option of renewing the contract at the end of the year, if contractor performance is satisfactory.

During the reporting period 67,981 trays of liquid scintillation vials, each containing 100 vials, were collected and packaged for disposal. The vials were packed with adsorbent material in 2,266 fifty-five gallon steel drums for burial. There is continuing concern regarding an alternative means of disposal of this very low-level waste as it uses a large volume of the available burial space at radioactive waste disposal sites. Another 700 drums of compacted radioactive solid waste and solidified liquids were also disposed of by burial.

Clinical Services

Health physics services were provided for 11 patients receiving therapeutic doses of radioactive materials, primarily Iodine-131. The services included radioassay of material administered, assistance with administration of the material, contamination control measures, steps to minimize personnel exposure, training and education of patients and patient care personnel, personnel monitoring, and determination of the patient's body burden for discharge and radiological protection purposes.

Laboratory and Environmental Surveillance

There were 5,257 radiation surveys conducted in laboratories using radioactive materials. Approximately 50 percent of the surveys were conducted by contract and the remainder by RSB staff. In addition, 4,469 air samples were collected and analyzed for radionuclide concentrations in laboratories and effluent air.

Efforts to establish a waste water monitoring system to determine radionuclide concentrations in NIH sewage effluent have been largely unsuccessful. This system is essential to provide assurances to the NRC that sewage concentrations and total releases of radioactive materials do not exceed applicable regulatory requirements. Currently, these values are derived by computation. The difficulty is with the long delays experienced in the procurement of a multichannel gamma spectrometer and associated computer and delays in designing and installing the sampling station. The former is needed for radionuclide identification and quantitative analysis, and the latter to assure that representative samples are collected proportional to sewage flow and also to monitor and record waste water flow.

Contractors made 129 surveys of X-ray equipment. In addition, 47 sealed sources or radioactive foils and 184 radium-226 needles were checked for leakage semiannually in accordance with License 19-00296-10. None of the tests indicated removable contamination greater than the action level of 0.005 microcuries.

Personnel Monitoring

Film dosimeters for the evaluation of personnel exposure to external sources of radiation are supplied and processed by a commercial source. The number of NIH employees on the monthly monitoring service increased from approximately 2,500 at the beginning of last year to 3,000 at present, a 20 percent increase. Approximately 400 of these individuals are also issued one or more extremity monitors in addition to the whole-body dosimeter. A total of 2,192 additions, deletions, or other film badge service record changes were required during the year. Employees at the Rocky Mountain Laboratory and two Arizona field stations are also covered by this service. Radiation exposure records are maintained for approximately 200 additional NIH employees working at other "off-site" locations.

There were 1,257 radioassays of urine from persons working with beta-emitting radionuclides. Although RSB has developed an automatic data processing system to review radionuclide receipts and generate requests to investigators for bioassays and whole-body counts, considerable staff time is required for followup.

Whole-body or thyroid counts were also requested for 572 authorized users and laboratory personnel working with gamma-emitting radionuclides. The evaluations are made by the Whole Body Counting Section, Nuclear Medicine Department, Clinical Center; it is estimated that approximately 2,400 separate in vivo measurements were made at the request of this Branch.

Radiation Safety Training

Approximately 13,000 hours of training were provided to over 1,000 NIH employees. In addition, a number of visitors from other agencies and NIH contractors attended the "Radiation Safety in the Laboratory" training course. Major training sessions and attendance figures are summarized below:

Course	Number of Times Course Presented	NIH Staff in Attendance	Visitors
Radiological Health for Radionuclide Users (9 days)	2	125	0
Radiation Safety Review for Authorized Users (1 ½ days)	4	76	0
Radiation Safety in the Laboratory (1 day)	12	599	79

Course	Number of Times Course Presented	NIH Staff in Attendance	Visitors
Radiation Safety for Nurses (1 hour)	6	97	0
Radiation Safety for Housekeeping Staff (1 hour)	1	125	0

In addition, radiation training courses were presented at the Rocky Mountain Laboratory, National Institute of Allergy and Infectious Diseases, Hamilton, Montana, and the Phoenix Clinical Research Center, National Institute of Arthritis, Metabolism, and Digestive Diseases. Branch staff also participated in several laboratory safety courses presented in various locations throughout the country by the Center for Disease Control and the National Institute of Occupational Safety and Health.

Other Radiation Safety Services

The laboratories in Building 21 were used to conduct 978 radionuclide experiments under the supervision of RSB health physicists. The experiments involved higher levels of radionuclide activity than are generally permitted in a typical NIH research laboratory.

A detailed evaluation was made of the shielding design for the proposed Diagnostic Radiology Department in the new Ambulatory Care Research Facility. Modifications were suggested to obtain the required level of protection at the most reasonable cost.

The Branch is working closely with the Nuclear Medicine Department, Clinical Center, in developing capability for a positron imaging program. The RSB will have input into the safety aspects of the procedures to synthesize and label compounds with the short-lived positron-emitting radionuclides. The plan is to initially obtain these radionuclides from cyclotrons located in the area. However, long-range plans will probably result in the installation of a cyclotron on campus.

PLANS

Additional emphasis will be placed on the following activities during the coming year:

1. Securing compliance with those items noted in the most recent NRC inspection. Specifically, improving the security of radioactive materials in unrestricted areas and developing more effective procedures to assure that new radiation workers receive proper radiation safety training before beginning work with radionuclides.

2. Implementation of a computerized Radiation Safety Management Information System in cooperation with the Division of Computer Research and Technology and the Office of Management Analysis, DRS.

3. Implementation of a waste water monitoring system to assure the NRC, Washington Suburban Sanitary Commission, and Montgomery County Government that radioactive materials that may enter the sewer system at NIH are below regulatory limits.

4. Developing plans for enlarging or modifying Building 21 so that it may be safely used for labeling compounds for positron emission tomography studies.

5. To the extent that resources permit, providing increased levels of surveillance and technical assistance to NIH employees working at locations other than the Bethesda reservation.

DIVISION OF RESEARCH SERVICES

LIBRARY BRANCH

October 1, 1977, through September 30, 1978

RUTH C. SMITH, Chief

The mission of the Library Branch is to operate an efficient comprehensive library in support of NIH research and administrative programs. The Library selects, acquires, organizes, maintains, and circulates literature pertinent to the programs and provides interlibrary loan, reference, bibliographic, translating, and copy services.

A new on-line search capability of scientific data bases of interest to NIH investigators was introduced by the Library during FY 78: The circulating journal collection was included in the Automated Circulation Control System, which has operated effectively for the book collection. Consultative surveys were provided the National Cancer Institute regarding facilities and future plans of the Scientific Library of Frederick Cancer Research Center, which is operated by Litton Bionetics for NCI. The Lemuel W. Diggs Collection on Sickle Cell Disease was presented to the Library by Dr. Diggs, noted pioneer in sickle cell disease research.

An acute space problem has necessitated drastic measures. In order to provide shelving space for 1978 journals, little used journals are boxed for storage elsewhere. Approximately 9,400 old, unused, and unneeded books have been eliminated from the collection, and some 68,000 cards representing them were withdrawn from the Library's catalogs. A major critical problem resulted from this summer's reroofing of the terrace outside the Library when, during and after rains, water dripped from multiple places in the ceiling in the Lower Level area where the monograph collection is located. Every attempt was made to prevent the books from being damaged.

PROGRAMS AND ACCOMPLISHMENTS

Technical Services

The operations of procurement, organization, and processing of books increased approximately 30 percent in FY 78. Contributing factors included a program to reduce work backlog and the attainment of a full professional staff. Operations for journals remained stable.

Books on bioethics were given a separate classification (R724) so that they may be shelved together. The section includes new acquisitions as well as volumes on the subject already held by the Library.

Bar coding of all circulating journals in the collection, recording the required bibliographic data, and entering the data into the Library's

Automated Circulation Control System were completed by the end of the fiscal year. Now circulating journals are loaned through an automatic procedure as books have been during the last two years.

The substantial project of changing or withdrawing Library records, computer file data, and catalog cards to reflect the status of books weeded out has continued for each batch as soon as decisions have been made.

Readers Services

Operations of circulation and nonprint media remained relatively stable. Self-service copy service increased slightly over the FY 77 level, and interlibrary loans to NIH investigators decreased by 30 percent. The decrease was due to the greater availability of volumes on the shelves. Shelving of new books and journals and those used by readers has been maintained on a current basis. Interlibrary loan requests from other libraries remained at the FY 77 level.

Lack of shelving space continues to be an acute problem requiring an enormous amount of volume shifting and the new activity of boxing as many little used journals as can be accommodated in the Library storeroom. Users are advised by signs on the shelves to make inquiries when such material is needed. A study is being conducted to obtain data on journal use for policy formulation relating to journal retention.

Reference and Bibliographic Services

A number of scientific data bases of interest to NIH investigators were made available for the first time by on-line computer access. This search capability, instituted in March, has been made possible by using the facilities of Bibliographic Retrieval Services, Inc. (BRS) through a Federal Library Committee contract with BRS. The Library can now search BIOSIS Previews from Biological Abstracts, Psychological Abstracts, ERIC (Educational Resources Information Center), NTIS (National Technical Information Service), and Pollution Abstracts, data bases not available in the past.

The long-term Monograph Weeding Project to remove old, unused, and unneeded books from the Library's collection, which was initiated in May 1977, has progressed from the A's into the RC classification. Approximately 9,400 volumes have been eliminated from the collection, after consultation with NIH investigators.

Requests for MEDLINE searches amounted to 16,000, an increase of 11 percent over last year. The number of "manual" bibliographies, those requiring search through pre-1966 literature not included in computer data bases, also increased. Approximately 5,000 computer-generated bibliographies were provided to investigators desiring current-awareness service which provides monthly bibliographies to update areas of interest. Approximately 14,000 questions were received at the reference assistance desks and over the telephone.

Translating Service

Requests for translating service numbered about 917, a decrease of 23 percent from FY 77. A breakdown of the requests reveals a 7 percent increase for written translations and a 33 percent increase in the number of words for the written translations. Decreases occurred in all other categories. Of the total translations made, 230 were oral, 19 recorded, and 587 written. Existing translations were located for 81 requests. Contractual firms prepared 361 written translations and Library translators, 226 (including translations of letters), with total words amounting to about 3 million. All contractual translations were reviewed for quality in the Library.

Training

Forty employees received a total of some 3,650 hours of training in 125 courses, seminars, and workshops selected to meet individual needs for development and improved performance on the job. Eight employees participated in 25 Upward Mobility College courses, and one employee attended Adult Special Education courses. Two library technicians in the three-year Trainee Program in the Technical Services Section completed on-the-job training and 880 hours of college-level training courses. Other on-the-job training courses designed for performance in special projects were provided within Sections.

Exhibits

Exhibits were displayed by the Library to observe National Library Week; Asian-American Cultural Week (featuring art works by Mr. Alfred C. Laoang, Medical Arts and Photography Branch, Division of Research Services); National Black History Week (showing art pieces from the Smith-Mason Gallery, Washington, D. C.); and Hispanic-American Cultural Week. An exhibit in celebration of the 180th Anniversary of the Public Health Service 1798-1978 was on display in conjunction with the official ceremony held July 26 in the Masur Auditorium. Other exhibits featured the Division of Computer Research and Technology publication, AMSOM: Atlas of Macromolecular Structure on Microfiche; results of research by the late Dr. Simon Rodbard on the Structure of the Heart; books and journal articles on Human Sexuality in Medicine for health professionals; computerized bibliographic services offered by the Library; and new books acquired by the Library. Art assistance for the exhibits was given by the Medical Arts and Photography Branch.

PLANS

A total library automation project will be undertaken with the assistance of the Management Analysis Office, Division of Research Services, and the Division of Computer Research and Technology. Included in the project will be most library functions that can be automated to provide more efficient service. They will include acquisitions, cataloging, serials management, circulation, interlibrary loan, and subject searching of an on-line catalog of library holdings. The automation project could result in making information about the Library's holdings more accessible to NIH researchers by placing terminals in the Bureaus, Institutes, and Divisions.

The Library is purchasing some of the more heavily used journal titles in microfiche format in an effort to improve its photocopy services. The microfiche for current and recent volumes will be used to print requested articles, while the hard copy of the issue will remain available on the shelves. Statistics on frequency of use, availability, and personnel time will be maintained to determine the overall effectiveness of this project.

The Monograph Weeding Project will be completed early in the next fiscal year. At that time a survey of the collection will be made to determine where it is weak relative to the needs and research requirements of the Bureaus, Institutes, and Divisions. Subsequent selections will reflect necessary changes.

PUBLICATIONS

Gillespie, C. J.: Drug Information Services. Adv. Pharmacol. Chemother. 15: 51-85, 1978.

National Institutes of Health Library: Audiovisual Materials Catalog Update. 1978 (Internal use only).

National Institutes of Health Library: Current and Noncurrent Journals in the NIH Library 1978. 1978 (Internal use only).

National Institutes of Health Library: Memorandum: Recent Additions to the NIH Library. Monthly (Internal use only).

DIVISION OF RESEARCH SERVICES

MEDICAL ARTS AND PHOTOGRAPHY BRANCH

October 1, 1977, through September 30, 1978

MR. ARTHUR F. MOORE, Chief

Requests for services of the Medical Arts and Photography Branch (MAPB) increased approximately 20 percent in FY 1978. The heavier workload was met by a corresponding increase in contract services. Delivery of finished artwork accelerated during the year. The time needed for normal photographic service remains at 5 workdays, but emergency requirements are handled in 24 hours. Graphic services are now also delivered within 5 workdays or, in emergencies, 24 hours. Design work is available in 10 workdays or, in emergencies, a fraction thereof as is consistent with quality. The graphics standards established for statistical materials produced by the Branch continue to be extended in application, the goal being a unified visual communications system for NIH. With new equipment, wider use of contract services, and training programs, the Branch will expand its skills and meet rising demands for services.

PROJECTS AND ACCOMPLISHMENTS

The objectives of the Branch are to provide consultation and production services to NIH; to visually communicate program efforts and research results; to provide skills and techniques in visual design, medical art, fine art, applied arts, still photography, and cinematography for solving problems of recording, communicating, and presenting research activity; and to investigate, develop, and upgrade visual techniques.

In meeting NIH research program demands, the Branch supplies professional services competitive with commercially obtainable services at the lowest possible cost. It develops specialized capabilities, particularly in graphic presentation, still photography, cinematography, and medical arts tailored to NIH needs.

The Branch monitors art and photography services procured by outside contract, serving as a technical adviser in obtaining needed additional services at the lowest cost consistent with high quality.

Programs of the Branch are still and motion picture photography, including photomacrography, photomicrography, cine photomicrography, high-speed cinematography, general photography, and related laboratory services; visual arts production including publications design and general graphics; visual aids including slides, vu-graphs, and other projectables; animation artwork; technical, general, and medical illustrations; exhibit design; statistical drafting; display charts; and medical models.

Increased demands for services were made of MAPB this year, climaxed by the intense activity created by the Federation of American Societies for Experimental Biology Meetings.

The graphic design manual prepared by the Branch to upgrade visual communications is being widely accepted. The manual is adding designs to accommodate greater statistical complexity, achieves uniformity of graphics quality, improves communications, and effects savings by establishing standards and eliminating preliminary design problems.

The Photography Section instituted technological improvements in the areas of photomicrography, photomacrography, and photographic laboratory services. The improvements were accomplished by formal technical training and attendance at seminars and professional meetings as well as by replacing old equipment with advanced photographic tools. Firm and fair leadership, imaginative management techniques, communication between first-line supervisors and employees, and appropriate training have enhanced employee morale and the quality of photography production in the Section.

The Photography Section extensively utilized outside vendor services from private photo firms in the D.C. area, in addition to in-house facilities, in order to keep pace with the ever increasing calls for photography services by the National Institutes of Health.

The Design Graphics Section possesses a nucleus of well-trained, extremely dedicated personnel. This group enables the section to respond to extraordinary requests for complex visual productions, which are continually mounting in numbers. The Section had a productive year, augmenting output 20 percent, with no increase in personnel and maintaining its usual high quality production. The Section has a spirit of pride in its ability to expeditiously handle any visual production requirement of the biomedical community.

Requests for medical illustrations remained at a normal level throughout the year. Contracting was seldom used since few projects entailed short deadlines. Calls for medical models remained about the same as in FY 1977.

The Motion Picture Section increased filming by 17 percent to an average of 4,230 feet per month and made several formal productions.

MAPB personnel spent 1,504 hours in formal training courses at a cost of $3,026.00.

In many instances, the NIH community still does not allow sufficient lead time for planning and execution of audiovisual materials. Needless demands for rush work deprive other NIH staff members of services they deserve. The Branch has extensive expertise in planning and conversion of raw data into effective multimedia presentations. The counsel is readily available in all areas of MAPB, or on location, and should be used earlier and with more frequency.

PLANS

The Medical Arts and Photography Branch will pursue the development and implementation of a system to upgrade NIH visual communications. It will aim to improve, enlarge, and extend its services and will seek additional ways to acquaint the NIH community with its skills. The importance of early counsel and planning, for optimum service, will be emphasized.

DIVISION OF RESEARCH SERVICES

VETERINARY RESOURCES BRANCH

October 1, 1977, through September 30, 1978

DR. ROBERT A. WHITNEY, JR., Chief

Projects carried out by the Veterinary Resources Branch during the year included production of 340,000 rodents, 1,000 purebred foxhounds, 620 rhesus monkeys, 81 goats, small numbers of inbred miniature swine, burros, and several species of nonhuman primates. Purchased rodents and rabbits more than doubled from 235,000 last year to 542,000 this year. Prior to India's April 1978 ban on exporting rhesus monkeys, 1,584 were acquired and quarantined. Small numbers of other primates, carnivores, ungulates, and fowl were procured.

Major renovations were completed on the central experimental surgery facilities in Building 14E, allowing the Branch to provide complete experimental surgical service to NIH investigators. The initiation of plasmapheresis techniques permitted supply of large quantities of plasma from domestic livestock without increasing the number of animals used.

Monitoring research animals for genetic type and microbiological contamination increased dramatically. The methods employed are becoming more and more sophisticated.

PROJECTS AND ACCOMPLISHMENTS

1. Animal Center Section

The number of foxhounds issued increased from 900 in FY 1977 to 1,050 in FY 1978. Therefore, it was necessary to purchase more foxhounds from the contractor (240 in FY 1977; 350 in FY 1978). No random-source foxhounds were obtained this year.

Rigid culling of aged nonproductive breeders has reduced the VRB colony by about 14 percent, from 176 to 150 bitches. The reorganization of caretaker responsibilities and increased emphasis on breeding problems have increased production to 1,000 dogs, a higher level than any previous year.

The inbred foxhound colony consists of one English and two American (Walker) lines in the third and fourth generation of inbreeding. Only the third and fourth generations are being retained in the inbred colony. Morbidity and mortality are increasing as the degree of inbreeding progresses. Histocompatibility typing and further red blood cell typing of the older inbred dogs retained for breeding have been completed. The results should facilitate evaluation of inbreeding progress and selection of breeding pairs. Histocompatibility typing will possibly be helpful in predicting the course of future breeding and circumventing deleterious results of inbreeding. These procedures are now being applied to our blood donor dogs to determine if some medical conditions have a genetic basis or tissue antigen predisposition. In the future, all

donor and breeding dogs will be typed to provide better defined animals and products. The work is being done in collaboration with the Canine Immunohematological Reference Center at Michigan State University.

The socialization program for colony-reared dogs is continually being refined to increase quality and efficiency. This program was initiated in 1976 to give puppies raised in our colony more experience with humans to prevent "cage neurosis" and fear biting. Investigators are requesting socialized dogs for some projects, and more researchers ask for dogs with specific behavioral and training characteristics.

All Carnivore Unit personnel are used to handle and leash-train puppies during the critical growth period in the breeding building (T-8). This has provided the optimum socialization time for dogs and the most efficient use of personnel.

Sufficient kennel space was available in FY 1978 to house an average of 160 experimental dogs on a long-term basis, equal to FY 1977. This service and increased production by the foxhound breeding colony have kept both dog kennel buildings and the dog pasture above desired capacity. Construction of a second pasture will alleviate occasional crowding. If not, long-term holding of dogs will have to be reduced.

Accurate prediction of dog utilization at NIH continues to be a problem. Issues this year unexpectedly increased 20 percent over last year; issues last year decreased 23 percent from FY 1976. Because of reduced requirements in FY 1977 and increased colony production, the contractor has had a surplus of dogs since February 1977 and has discontinued breeding. This surplus of dogs filled part of this year's increased demand. Additional in-house production has been limited by whelping and growing space. Therefore, if demands increase further, the requirement for purchased dogs may continue. Completion of a new paddock and installation of new whelping boxes will help alleviate the space problems, permitting in-house production of the NIH's total anticipated requirements for foxhounds.

The goat breeding herd was increased to 40 head of does and 2 buck in the Johne's disease free herd and 20 does and one buck in the conventional herd. During the spring of 1978, 51 does raised 84 kids. Goats from the breeding herd will be held until approximately one year of age before issue. We will then be able to provide investigators with healthy, good quality goats of known age and genetic background.

The number of inbred swine maintained and bred for the National Cancer Institute (NCI) has increased to about 140 head. Two temporary swine buildings with controlled environment were purchased and erected near Building T-3. The existing building at Three Springs Farm was moved to the same location. These buildings will allow the expansion of the swine herd to over 300 head. One building will be used for farrowing and as a nursery, another for rearing, and the third for long-term holding.

Primates, cats, ungulates, and feral animals are purchased and conditioned. These animals are not well defined genetically or microbiologically. Although of lower quality than NIH-bred animals, they are satisfactory for certain

studies. During a quarantine period, before release for use in research programs, the animals are given appropriate immunizations, tested for a variety of infectious agents, and treated medically as required. The Primate Unit animal records are now on a computer system. Information on any animal ready for issue is available through Automatic Data Processing. The system is also providing quarterly and epidemiologic reports.

India stopped all exports of rhesus monkeys in April 1978, which has caused a severe shortage of animals for research and polio vaccine testing programs. Other sources of supply are being sought. Bangladesh is a possibility. Investigators have been encouraged to use the cynomolgus monkey as a replacement; however, few have changed to this species because baseline data on the rhesus monkey have been established. Issues of rhesus monkeys are estimated at 2,200, a slight increase from FY 1977.

Monkeys of other species (Erythrocebus patas, Saimiri sciureus, Cercopithecus aethiops, Aotus trivirgatus, and Saguinus sp.) contributed small numbers to the quarantine and conditioning program. With the consent of investigators involved, a few owl monkeys and marmosets were kept as breeding pairs. Several births have resulted.

The Hazleton monkey breeding contract has been terminated and the animals transferred to the Bureau of Biologics (BoB). The other two breeding colonies will supply approximately 800 animals per year, which will eventually meet all NIH intramural requirements.

Construction has been started on the New World facility in the "300" corridor of Building 103 for holding research animals and the study of reproductive physiology. Approximately 25 pairs of owl monkeys, two harem groups of 12 owl monkeys, and one group of talapoin monkeys are now being held for this project.

Increased holding of marmosets and squirrel monkeys from the Peruvian breeding facility was undertaken. A small harem breeding group of squirrel monkeys was maintained for the National Institute of Allergy and Infectious Diseases (NIAID). A group of owl monkeys is also being held for NIAID in a paired configuration. Several owl monkeys are pregnant.

The fluid situation with rhesus monkeys, considering the Indian cutoff, fluctuating issues to BoB, and alterations in breeding programs create difficulties in setting rates and maintaining a balanced financial situation in the primate revolving fund. It is anticipated that FY 1979 prices will be approximately 10 percent higher to support breeding efforts and cover increased costs for feral monkeys, if obtainable.

Requests for random-source cats continued at the same rate as in previous years (800). A number of cats were vaccinated with a new product for two respiratory diseases, feline rhinotracheitis and calicivirus, but it did not appear to be beneficial. Ten ferrets were quarantined.

Ungulates are held under observation during investigative studies. Physiological sampling and specimen collections are provided in association with these

studies. Holding facilities are also available for the long-term observation of nonhuman primates.

Surgery and radiographic facilities for experiments on ungulates include modern equipment for restraint, anesthesia, and physiologic monitoring under aseptic conditions. Postoperative care is provided. Although investigators infrequently perform ungulate surgery, the facilities are used regularly by VRB staff for clinical and surgical procedures required by VRB programs.

The number of radiographic exposures in Building 100 decreased due to the installation of portable units in Buildings T-8 and 103. Also, the National Institute of Child Health and Human Development program requiring radiographs of pregnant ewes has been discontinued. The automatic film processor continues to be used by all areas.

Production of biologicals is an important VRB responsibility. A colony of foxhounds with the blood type Dog Erythrocyte Antigen 1 and 1.2 negative supplies normal canine blood for use in experiments. The 240 dogs in the donor colony produced 3,000 units of blood (1 unit = 500 ml) this year whereas 3,700 units were issued in FY 1977. This is the first year a sizeable reduction has occurred. Health problems due to increasing age appeared in the colony in FY 1977 and 1978. A culling program is reducing the colony to a number consistent with the lower blood issues. The program will provide kennels for housing more colony-raised dogs and some breeding bitches.

Ungulates are maintained for production of antisera, normal blood, and tissue specimens. There was an increase in production, the total being 1,650 liters of ungulate blood. The increase was due partially to a new service made available in November 1977, which utilized a Haemonetics Model 30 Cell Separator Blood Processor to provide the capability of automated plasmapheresis for horses, burros, sheep, and goats. This procedure provides investigators with a method of harvesting greater quantities of plasma than is possible with conventional bleeding procedures. A total of 200 procedures per year was projected, but during the first six months the service was available, 180 procedures were performed: 12 horses 40 burros, 89 sheep, and 39 goats.

2. Comparative Pathology Section

During FY 1978 emphasis was put on recruitment and training of personnel, updating of genetic profiles, and collaborative research projects. New laboratory facilities, originally scheduled for completion in March 1978, should be available by early fall.

Monitoring the genetic integrity of inbred mice is accomplished by testing for groups (profiles) of characteristics (markers) which identify the genetic consitutions of each strain. The profiles consist of morphological, immunological, and biomedical markers of 30 loci on 15 of the 19 mouse autosomes. The profiles are used in investigations of suspected genetic contamination of animals in NIH laboratories. Research is aimed at refining and developing new marker systems and establishing profiles for use in monitoring additional animal genera.

Over 2,500 assays were performed, although lack of adequate work space precluded establishment of a routine surveillance program for the mouse colonies. Approximately 800 assays were made to monitor NIH mice, while 1,700 were for research purposes. In addition, programs were initiated to extend genetic monitoring to inbred strains of rats.

A major genetic contamination occurred in the BALB/cAnN strain of mice raised at NIH and was investigated by characterization of seven isozyme markers. Comparison of these data with the genetic profiles of mice maintained by the Small Animal Section revealed that many were BALB/cAnN X NZW/N F_1 hybrid animals. As both these strains are albino, the contamination was demonstrated through the use of biochemical markers. Although no F_2 or backcross animals were detected, the contamination was found in both the expansion and production colonies, and some contaminated mice had been shipped to investigators. BALB/c mice in these colonies were destroyed, and the strain will be re-established with offspring from the pedigree expansion and foundation colonies. No contamination has been found to date in these latter colonies, although progeny of all breeding pairs are being examined to ensure their genetic purity. The monitoring laboratory has been examining, on a limited basis, putative BALB/c mice sent to investigators before discovery of the contamination.

The monitoring service was asked to identify the strain of 15 black mice in C-wing that were found dead in a cage marked "CBA." The cage also contained live agouti mice, presumed to be of the CBA strain. The dead mice were believed to be either NZB or C57BL/6, based on information provided the Small Animal Section. Typing for 5 enzymes on 4 chromosomes failed to identify these mice as any of the 45 inbred strains maintained by VRB. Hemoglobin typing was inconclusive. Blood samples for analysis were obtained from heart clots from two animals estimated to have been dead four to eight hours. A conspicuous autopsy finding was brain edema, but the cause was not determined.

An aberrant coat color was noted in the DBA/2 strain of mice raised at the Frederick Cancer Research Center (FCRC). A genetic profile of the mice was made and compared to that of DBA/2 animals at NIH. Morphological and biochemical analysis revealed that the suspect animals were not genetically contaminated and that the aberrant coat color was probably the result of a point mutation at the locus.

Several collaborative and advisory activities were initiated on international, national, and local levels. At the request of the Central Institute for Experimental Animals in Japan, the genetic monitoring laboratory is providing assistance in establishing a genetic surveillance laboratory in that country. In turn, we will acquire access to a large number of additional strains of mice, thereby substantially increasing our ability to map the mouse genome.

Many inbred mouse strains maintained by VRB have been typed for the lymphocyte cell surface antigens Lyt-1, Lyt-2, and Thy-1 as a result of a collaborative program between the laboratory of Dr. E. A. Boyse at Memorial Sloan-Kettering Cancer Center and our genetics program. Facilities and personnel will soon be available to extend the typing. Collaboration between the two laboratories has resulted in the mapping of the lymphocyte cell surface antigen Lyt-4 on mouse

chromosome 1, which permits the use of this marker for genetic surveillance. Other projects to map additional immunological markers are in progress.

The genetics laboratory is also performing quantitative catalase assays on mouse cells grown in vitro as part of a joint study with investigators in the National Cancer Institute. Following periodic exposure to light of relatively long wave lengths, the cultured cells are examined for malignant transformation, chromosomal abnormalities, and levels of the enzyme catalase. Catalase lowers the levels of intracellular hydrogen peroxide--a possible mutagenic agent. Decreased levels of catalase may, therefore, correlate positively with malignant tranformation.

Staff pathologists and microbiologists aid in control and elimination of disease in NIH animal colonies. Disease problems in a wide variety of animals are dealt with in conventional, germfree, and barrier-sustained colonies. Monitoring for many microbial agents and parasites is performed routinely.

Research on the pathogenesis of naturally occurring diseases in laboratory animals is conducted to facilitate both diagnosis and control. Laboratory assistance, training, and administrative liaison are provided for animal disease investigators concerned with the control of diseases in NIH research laboratories. Tissue processing services also are provided.

Staphylococcal subcutaneous abscesses became a serious problem in barrier-maintained nude mice during the year. The disease spread to three of the four rooms for these mice, and 206 mice with lesions were killed. The abscesses were facial in most of the mice (98.5 percent) but also occurred on the trunk (14 percent), limbs (1 percent), and in the preputial glands (2.5 percent). Of the affected mice, 64 percent were male. The age range was 5 to 59 weeks, the average being 21.5. Although all strains of mice appeared to be susceptible, the NFS strain had by far the highest incidence. Coagulase-positive Staphylococcus aureus was repeatedly isolated from the abscesses and from feces of affected mice. Studies by the Environmental Safety Branch revealed heavy staph contamination of water bottles, feeders, and walls of cages in the affected rooms. Nine isolates (eight abscesses and one fecal) from the three rooms were submitted to the Center for Disease Control and found to be nontypable by the International Series of staphylococcal bacteriophages, used in typing human isolates. Three isolates from personnel closely associated with the mice were type 53/83A. Thus the findings indicate that the staphylococci examined were not cross colonizing between humans and mice. Nevertheless, one of the obvious ways that the causative organism could have gained entry into the barrier is by transiently contaminated animal care personnel. Other ways include introduction in improperly autoclaved feed or equipment and intra-uterine transmission.

Cecitis in C-wing rabbits continued to be a major problem, resulting in 202 deaths. The cause is still unknown, although previous studies suggest that the disease may be due to imbalances of intestinal microflora and exacerbated by antibiotics. Since a rotavirus was reported in rabbits with diarrhea in England in 1976, an effort was made to demonstrate such an agent in the rabbits with cecitis. In collaboration with NIAID investigators, fecal filtrates from many rabbits were clarified and examined for viral particles by electron microscopy and immunoelectron microscopy. No viral particles were found. An

electron-microscopic search of sections of cecal mucosa failed to reveal viral particles or other etiologic clues. Rabbits free of the disease are being produced in order to compare the microflora of these animals with that of the diseased ones.

Johne's disease was confirmed histopathologically in 21 goats, and for the first time was also found in a sheep. The disease is extremely difficult to eradicate; the causative organism is relatively stable in the environment, and detection of it in animals incubating the disease is laborious. Goats or sheep may incubate the disease for several years before fecal cultures reveal the causative agent. The disease is considered to be endemic in Maryland goat herds. Current efforts to eliminate the disease from VRB herds are focused on isolating newborn animals for development of a nucleus of disease-free breeding stock. The newborns are prevented from nursing and protected from contact with contaminated environment before being removed to an isolated location and fed on milk replacer. Although colostrum is fed initially, it is acquired by hand milking after Betadine disinfection of the udder.

Studies were conducted to determine which disinfecting agents may be effective against the spores of Bacillus piliformis, the causative agent of Tyzzer's disease. Of a host of common disinfectants tested to date, only chlorine and peracetic acid have been shown to be effective. Ten percent formalin was ineffective. Previously, it has not been known which agents should be used to eliminate spores from animal rooms after Tyzzer's outbreaks, or to clean up work areas where the agent has been used experimentally.

An outbreak of canine tracheobronchitis affected 25 percent of the puppies born at the Animal Center during late winter and spring. Approximately 5 percent of these died after prolonged illness. Pathology studies showed that the animals died of severe necrotizing bronchopneumonia. A variety of bacteria was isolated including Hemophilus, Bordetella bronchiseptica, group G streptococci, E. coli, and Streptobacillus moniliformis. Sensitivity studies indicate that resistance of the organisms to a number of antibiotics is interfering with therapy.

An outbreak of tuberculosis in rhesus monkeys resulted in 16 deaths over a 3-month period. It was found that these animals were in holding compounds in India for an unusually long time before shipment. Experience has shown that prolonged holding often will increase the prevalence of TB, as well as other diseases in incoming monkeys.

"Nonspecific deaths" over a long period of time in barrier-maintained guinea pigs were finally diagnosed as chronic scurvy, caused by borderline deficiency of ascorbic acid. Diagnosis was based on histologic changes in long bones, the frequent occurrence of intestinal hemosiderosis, and a history of feeding practices (autoclaved feed) which led to ascorbic acid deficiency. Scurvy was also diagnosed in guinea pigs at two Institutes. In one case, prolonged storage of the feed in a hot furnace room apparently lowered the level of vitamin C in the feed.

Last year one of the more serious potential problems related to introduction of Syrian hamsters into Building 37 from a laboratory in Tennessee. The

receiving investigator was informed several months later by the source that the hamsters might be infected with a highly contagious disease termed infectious lymphoma. Reports in the literature indicate that the causative agent is extremely difficult to eliminate from contaminated animal rooms. All suspect hamsters in Building 37 were killed and carefully examined for evidence of lymphomas. Utmost precautions were taken to prevent spread of the agent. Fortunately none of the suspect hamsters had lymphoma. One hamster had a subcutaneous anaplastic sarcoma in the anterior cervical region. The sarcoma was an incidental finding unrelated to infectious lymphoma in hamsters. In order to confirm the absence of the infectious lymphoma agent in Building 37, sentinel animals were placed in the rooms that had housed the suspect hamsters. Adult male and gravid and nongravid hamsters from an uncontaminated source were used. After 7 months, the sentinel hamsters were killed and examined. No evidence of disease was found. This type of disease problem demonstrates the need for some type of central quarantine system for animals brought to NIH from other locations.

A serious outbreak of streptococcal lymphadenitis occurred in a large laboratory colony of Strain 2 guinea pigs in one of the Institutes. This disease, caused by S. zooepidemicus, is considered difficult to eradicate therapeutically, especially in densely populated rooms. The disease first appeared as conjunctivitis; lymphadenitis was observed later. The disease was contained with antibiotics until several important short-term studies were completed. Then the colony of approximately 1,500 animals was sacrificed. Afterwards the facilities were thoroughly decontaminated and the colony repopulated. Retrospective investigations suggest that the causative streptococcal agent gained entry into the colony in contaminated tissue from a transplantable tumor provided by another laboratory.

An epizootic of fatal pneumonia took place in a rat colony housed in a contract holding facility. In the first four days, 53 animals suddenly became dyspneic and died. A number of laboratory studies were conducted to determine the cause of the rapid and frequent deaths. Most of the animals had severe leukopenia. Autopsies revealed typical lesions of chronic respiratory disease. Mycoplasma was isolated from the middle ear, trachea, and lungs of most of the animals. Pathogenic bacteria were absent in the same areas. Serologic studies revealed high antibody levels to pneumonia virus of mice and variable levels to Sendai virus. The collective data, including histologic findings, indicated that the probable cause of death was acute Sendai infection superimposed on chronic respiratory disease due to Mycoplasma. After the epizootic subsided, the mortality rate in the rat colony declined precipitously. Enzootic mycoplasmal pneumonia continued unabated in the colony. Death rates remained low for approximately 6 months. Then sudden deaths occurred again, as in the earlier epizootic. The chemical, microbiological, serological, and pathological pictures were identical. Fortunately, the later epizootic was on a much smaller scale. Measures are being taken in the colony to prevent further recurrence of the problem.

Hyperplastic colitis was diagnosed in mice at NIH for the first time. This naturally occurring bacterial disease of mice is caused by Citrobacter freundii.

The disease is characterized histologically by severe hyperplasia and varying degrees of inflammation along the colonic mucosa. The affected animals first exhibit general debility. Later the anus becomes swollen and excessive moisture collects around the perineum. Rectal prolapse may occur, but diarrhea is not a feature of the disease. Autopsies revealed typical lesions, and C. freundii was cultured from all the affected animals. Animals that recover may remain in poor condition or exhibit no untoward effects. At NIH the disease occurred simultaneously in two laboratories in separate buildings, but they were collaborating in a common study. How C. freundii was initially introduced was not determined.

Other infectious diseases in small animals were investigated during the year, Sendai pneumonia in mice was diagnosed in several Institutes. Three laboratories had small scale outbreaks of middle ear infection in mice, caused by Pseudomonas aeruginosa. The disease was controlled by acidification of the drinking water. Middle ear infection was also observed in several rabbits. These infections were due to Pasteurella multocida.

Canine distemper was diagnosed histologically in an experimental colony of young dogs belonging to one of the Institutes. Later serologic determinations indicated that some of the unvaccinated litter pen-mates had low antibody levels to distemper virus.

Listeriosis was detected in some sheep submitted for autopsy. They were from a farm which provided sheep for one of the Institutes conducting cardiopulmonary studies.

Limited monitoring of animals produced under contract for the BID's is continuing. This program was initiated in FY 1977. Animals to be tested are purchased from different suppliers as part of routine orders to avoid bias in selecting the animals by the suppliers. Because of manpower shortages and the need for practicality, the samples of animals are small and not necessarily proportional to the sizes of colonies from which they are derived. Also, no effort is made to regulate the location of sampling in rooms or buildings. The monitoring is limited to tests for salmonella, ecto- and endoparasites, and certain murine viruses. Viral testing (serologic) is performed by a commercial contractor. As in the previous year, the results indicate that the rodents from all the suppliers have antibodies to one or more viruses that cause disease problems and interfere to varying degrees with research in NIH laboratories. For example, antibody to Sendai virus or pneumonia virus of mice or both had been found in rodents from all five of the major suppliers being tested. Heavy mite infestations were found in one supplier's animals, and pinworms were found in another source.

Studies to detect microbiological contamination of mouse embryo tissue cultures were conducted for one of the Institutes. Chronic problems with apparent fortuitous contamination resulted in cytopathic effect (CPE) in the cultures. A slow-growing, gram-variable, non-spore-forming rod, probably belonging to the coryneform group of bacteria, was cultured and proved to be the cause of the CPE. Mycoplasma, a common contaminant of tissue cultures, was not found.

3. Small Animal Section

Rodents and rabbits are bred and reared in the Section colonies. Some are characterized genetically and some are microbiologically defined. Care is taken to maintain the genetic integrity of inbred strains and minimize the inbreeding of random-bred stocks. Germfree and specific pathogen-free (SPF) rodents are produced for intramural research programs and as replacements to enhance breeding and genetic colonies.

Rodents and rabbits are procured through contracts to augment in-house production and are delivered directly to NIH investigators. Quality control of these species is maintained through monitoring of the producers' facilities and operations by Branch staff members.

Germfree rodents are held for varying periods of observation while under test by investigators. Provision is made for physiological sampling and collection of specimens.

The professional staff consists of specialists in laboratory animal medicine, epidemiology, nutrition, genetics, and animal husbandry. All efforts are oriented toward improving the Section's programs by gaining new knowledge through research and assuring the health and genetic quality of procured and produced animals. VRB furnishes investigators with the information and assistance required to solve problems relating to animal experimentation, health, nutrition, care, and husbandry.

About 340,000 VRB-produced rodents and rabbits were issued to investigators, significantly less than last year. There was a decreased requirement for VRB inbred and noninbred mice, inbred rats, rabbits, and hamsters. The decline in inbred mouse utilization was expected because production of three major strains (BALB/cAnN, C57BL/6N, and DBA/2N) and a hybrid (BALB/cAnN x DBA/1N) was contracted through Division of Cancer Treatment, NCI. With few exceptions, demands for VRB strains and stocks of mice were satsified. Approximate animal issues were as follows:

Inbred mice	164,284
Noninbred mice	124,403
Inbred rats	7,726
Noninbred rats	21,093
Inbred guinea pigs	11,300
Noninbred guinea pigs	6,544
Hamsters	3,384
Rabbits	473
Germfree rats	345
Germfree mice	1,916

The FCRC continued to rely on VRB foundation colonies as the genetic base for their rodent colonies. Pedigreed mouse and rat strains were supplied from both the VRB barrier-maintained and germfree colonies. VRB has also assumed the responsibility of maintaining the genetic base for a variety of other NCI contract programs requiring germfree pedigreed stock and breeding nuclei of mice. This is the third year DCT has utilized this service.

The total purchase of rodents and rabbits from contractors greatly increased, from 235,000 in FY 1977 to approximately 542,000 this year. Much of the increase may be attributed to new contracts with DCT for mice and rats.

Animals purchased on contract are as follows:

Rabbits--Dutchland, Jackson and Charles River	7,875
Sprague Dawley Rats--Taconic	46,200
Hamsters--Lakeview	10,800
Swiss Mice--Taconic	34,300
Rats--ARS Sprague Dawley	8,650
Rats--Charles River	20,700
Rats--Microbiological Assoc.	16,300
Mice--Charles River	11,860
Mice--ARS Sprague Dawley	3,730
Mice--Microbiological Assoc.	1,460
Mice--Jackson Laboratories	117,200
Hartley Guinea Pigs--Dutchland Charles River	6,825
Mice--DCT	249,640
Rats--DCT	4,070
Hamsters--DCT	2,920

Breeding nuclei from the genetic resource are supplied not only to intramural investigators but also to the international biomedical research community since many of the stocks, strains, and substrains are not available elsewhere. The World Health Organization has designated VRB as an international collaborating center. The VRB was also designated an International Nude Mouse Reference Center in 1978 by the International Committee on Laboratory Animals.

Investigators at 291 institutions were provided with 8,136 inbred and noninbred animals to start breeding colonies. The figure includes 5,077 mice, 2,508 rats, 515 guinea pigs, and 36 rabbits. Several commercial producers were also provided with breeding stock.

VRB obtains or develops new animal models to meet previously unfilled research needs. Modifications were made in the health monitoring program to reduce the

time required to introduce new strains/stocks into the genetic resource without sacrificing standards. Three new strains were added at the request of NIH investigators. They were the BHE rat and ABL and Wobbler mice.

The following animals have been received at the rodent isolation facility and are in the process of being introduced into the resource.

MICE	RATS	GUINEA PIGS
C3H/Hej	A207	OH3
C3H/He-Avy	RCS	R9
C3HFB/He-Avy	RCS-cc	
C57BL/6J-lit	RCS-CC	
	Nude (rnu)	

Three inbred mouse strains were eliminated from the resource because they had not been utilized by BID's for 2 years. They were SPM/N, NBL/N, and BDL/N.

The ongoing program to introduce the nude gene into 21 strains of inbred mice is progressing well. This effort is being expanded to include congenic strains, with the subsequent formation of double congenics. A major effort is underway to develop a series of immunodeficient mouse models and controls, including mice with normal T and B cell function; normal T and defective B; normal B and defective T; and defective B and T systems.

Three families of recombinant inbred (RI) strains of mice are being developed. The combinations involved in this strain are C57BL/6N x CBA/CaHN, NFS/N x NZB/N, and C57BL/6N x C3H/HeN. Other models currently being developed in response to BID needs involve the mutant genes dwarf, beige (Chediak-Higashi syndrome), and motheaten (hypergammaglobulinemia/hyperautoimmunity) genes. Characterization of an autosomal recessive mutation in the SJL-nu congenic is being pursued. This mutation, independent of Nude, affects development of the undercoat. An effort was undertaken to identify N:GP(s) mice which are non-responders to B-cell antigen. The responsible gene apparently exists in high frequency, and the ultimate goal is to develop an inbred strain carrying it.

Evidence of a major gross genetic contamination involving the BALB/cAnN and NZW/N strains was found by an animal caretaker and confirmed by biochemical testing. The contamination, apparently caused by human error, occurred in the expansion colonies and was propagated in the production colonies. Affected colonies were eliminated and repopulated from the foundation stock. Genetic contamination of the congenic C57BL/6N-me also occurred. The trait (motheaten) has been re-established into unaffected C57BL/6N mice.

Animal model development utilizing the rat colonies is progressing satisfactorily. The corpulent gene is being introduced into hyper- (SHR/N) and normotensive (LA/N) strains to permit studies of the relationship of corpulence to blood pressure. Similarly, the diabetes insipidus gene is being introduced into normo- (RHA/N and hypertensive (SHR/N) strains. In response to BID requests for the jaundice gene in defined rats, it is being established in the inbred strains RHA and ACI.

Efforts to develop acceptable pathogen-free rabbits continue. Although the animals are free of the common rabbit pathogens, including Bordetella, Pasteurella, and Eimeria, mortality from cecitis is excessive. We also are continuing attempts to develop pathogen-free, noninbred guinea pig colonies in the barrier. Because of severe reproductive problems, maintenance of inbred guinea pigs in the barrier was discontinued. The number of germfree isolators available for research use by investigators was increased from seven to twelve.

A program to provide cesarean-derived, germfree swine, including technical support for maintenance and research, was initiated. Closure of FCRC inbred guinea pig colonies resulted in heavy demands on the Section's colonies. They are being partially met by expanding the colony sizes.

The quality assurance program for animal feeds used at the NIH was reviewed, and feed assay requirements were modified. Assays for estrogen concentration were discontinued and replaced with the requirement that each batch of purchased feed be assayed for nine potential contaminants. The rationale was that virtually all feed samples assayed for estrogen during the past 10 years contained less than the 4PPb acceptable maximum concentration, while increased concentrations of pesticide residues and heavy metals have been reported with increasing frequency. Monitoring the concentrations of these compounds in animal feed is necessary to maintain the quality of NIH testing and research programs.

Numerous investigators from NIH and other research institutions sought advice regarding experimental diets for laboratory animals. During the past year, approximately 30 new diets were formulated and over 40 modifications were made in existing diets to accommodate specific research projects. Increasing numbers of institutions throughout the biomedical research community are using the NIH open-formula diets as standards. Most major companies that manufacture feeds for laboratory animals routinely make the NIH open-formula diets available to their customers.

The results of nutrition experiments involving nonhuman primates showed that a 4 percent increase in dietary crude fiber would practically eliminate digestive disorders that occur in newly imported rhesus monkeys. Contract arrangements have been made to purchase experimental nonhuman primate diets for a series of studies required to develop open formulas for these species.

Data collected from 64 rat and mouse foundation colonies fed the NIH open formula autoclavable diet (18 percent crude protein) for 2 years indicate an increase in the reproductive performance of most strains as compared to the previous 5 years when they were fed a commercial diet (24 percent protein). A study conducted in the colonies of an NIH contract breeder indicated that reproduction in rats also improves when an autoclavable commercial feed is replaced by the NIH open formula. The use of the open-formula diet at contractor facilities is advantageous because of the increased nutritional uniformity between animals produced by NIH colonies and those purchased from contractors. In addition, use of these diets reduces feed cost by about 30 percent.

Reproduction decreased when the diet of the inbred guinea pig colonies was

changed from a commercial feed to an open formula. After a period of adaptation, however, reproduction is nearing normal levels. It appears that these particular strains are sensitive to any dietary change and that the open formula is not nutrient deficient.

Depressed reproductive performance among certain strains of rats and mice was apparently related to seasonal (winter) changes. One mouse strain (STAR/N) was nearly lost, and considerable effort was required to maintain the others in a productive capacity.

A coordinated effort was begun to eliminate pinworms and ectoparasites from the production colonies. The frequency of Piperazine and dichlorovos treatment was increased and extended. Concurrently, the facilities were scrubbed, disinfected, and treated with a long-acting organophosphate. Results to date indicate that mite and pinworm populations are markedly reduced. The nature of the facilities and the logistics involving cages and equipment, however, make it unlikely that the problem will be resolved permanently without a continuing eradication program.

Four rabbits died from Tyzzer's disease early in the year. The outbreak was halted by treating all rabbits in the colony with tetracycline in the drinking water.

Automatic watering systems used in the rat colonies function poorly because the hydrochloric acid mixed with drinking water to prevent introduction of disease into the barrier is extremely corrosive.

The disparity in pay between biological laboratory technicians working in the barrier and animal caretakers working in conventional colonies is not resolved. It results in a situation where more technically skilled workers are paid less than those performing less skilled work, which results in recruitment difficulties and poor morale. It will be difficult to effect program changes involving increased emphasis on highly technical programs if this situation continues.

4. Veterinary Medicine and Surgery Section

Following is a list of current research projects:

Attempted induction of idiopathic hypertrophic periostopathy in a dog by administration of plasma from a man with the same disease. (To date, the condition has not developed in the dogs.)

Composition of an atlas for aging fetal monkeys by assessing skeletal development of the carpus.

Induction of brain lesions in fetal monkeys to study the regenerative process of neurons at early stages.

Increasing the susceptibility of monkeys to malaria by surgical removal of their spleens.

Induction of diabetes melitus in rhesus monkeys by injection of measles virus into the pancreas and aorta.

Studying the pattern of collateral coronary blood flow after acute coronary occlusion followed by treatment with nitroglycerin and methoxamine.

Evaluating the effects of aspirin in modifying gross infarct size as determined by infected tissue compared to total myocardium at risk.

Evaluating the effect of exercise on the development of atherosclerosis in miniature swine (Yucatan) fed a high-cholesterol diet.

Testing a miniature fiber optic pH sensor suitable for in vivo application in man.

Evaluation of experimentally induced infarcts by the use of various radioisotopes.

Induction of hypertension in animals by use of surgically implanted silicone that has been impregnated with desoxycorticosterone (DOCA).

Measurement of melatonin in cerebral spinal fluid in an anesthetized monkey over a 24-hour period. After destruction of the suprachiasmic nucleus, a study will be undertaken to determine where melatonin is actually produced.

Inoculation of fetal guinea pigs with oncongenic viruses in an attempt to produce tumor models in guinea pigs.

Performance of cesarean section in adult sows in an appropriate manner to obtain gnotobiotic piglets to study a rotovirus that causes diarrhea in human infants.

The comparative medicine unit continues to increase its scope of research animal holding. The average monthly inventory ranges from 300 to 350 animals, including six species--the dog, cat, pig, sheep, goat, and calf. In addition to routine large animal holding, metabolic cage and controlled environment holding is available for infected and cesarean-derived large animals.

Two metabolism cages to hold minipigs were installed and are being used to support DOCA studies. The cages allow for the collection of animal urine and feces so that absorption, elimination, concentration, and metabolic turnover of DOCA can be assayed. The pig is proving to be an ideal model for these investigations, which are designed to correlate hemodynamic changes, blood pressure, and sodium, potassium, and water balance. Cesarean-derived pigs are held in germfree isolators to support the rotovirus studies mentioned above.

Facilities are provided to hold cats received from various sources that are infected with leukemia virus. The cats are placed in isolated cages to contain and prevent spread of the infection to other cats.

The primate reuse program is fully operational and has been well received by

BID investigators. During the year, 153 primates were accepted for reuse and 78 were issued. The increase in demand may be related to the embargo imposed by the Indian Government in April, which prohibited exportation of primates from that country. The holding capacity of the Primate Research Unit is over 1,000. It does not totally satisfy all demands. About 350 primates were added during July.

While 20 females were added to the VRB rhesus timed-pregnancy breeding colony, 40 were added to the contractor's breeding colony. The additions have led to an increase in the number of pregnant monkeys available for use by investigators. During the year, 81 timed-pregnancy rhesus were issued, and 18 pregnant baboons were issued and housed. The timed-pregnancy baboon contract was allowed to expire in July due to lack of interest by BID users.

The surgical facilities are intended primarily for use by BID investigators. However, surgery is frequently performed by staff veterinarians in support of BID programs requiring particular surgical animal models. Assistance in anesthesiology, diagnostic radiology, and postoperative care of animals is also provided to investigators. A 500 milliampere radiographic unit with fluoroscopy is available. Radiographs of primate fetuses can be made during surgery.

Despite the inconvenience of renovation of relocation of the surgery unit during the past year, approximately 350 surgical procedures were accomplished. They included numerous thoracic, cardiovascular, fetal, neurosurgical, and abdominal procedures demanding a high level of technical support. Surgical assistance was also furnished for malaria studies, induction of cancer in guinea pigs, skin grafts for immunological studies, and collection of cerebral spinal fluid for measurement of melatonin. Greater professional and technical assistance to the BID's during the past year has improved surgical animal models and veterinary medical care. Surgery during the past year included procedures on dogs, cats, guinea pigs, rats, hamsters, monkeys, rabbits, and pigs.

PLANS

1. Animal Center Section

NIH dog production has increased substantially this year and is expected to replace the need for contract dogs as the puppies reach issuable ages in FY 1979. Two wings will be added to Building 102 to improve facilities for the foxhound breeding colony. Arrangements have been made to purchase a limited number of purebred English foxhounds from the colony at Ohio State University.

Pneumonia is still the major health problem in young, lab-reared dogs. The old wooden whelping boxes may harbor causative organisms and will be replaced. New whelping boxes made of knockdown Bakelite panels have been designed and ordered. They can be cleaned and sanitized more efficiently, will utilize radiant floor heat more effectively, and will provide flexibility in the whelping wing.

An automated data processing system being developed for the carnivore breeding

colony could be used also for other animal populations in the carnivore unit. It should be operational in about a year.

The goat, minature swine, and burro breeding herds will continue to expand. Health surveillance of ungulate herds and flocks will be expanded and intensified. Emphasis will be placed on identifying goats and sheep with Johne's disease and eliminating them from the herd.

A large pole barn is planned for the pasture area north of Building 100. Sheep now housed in Building 100 will be moved to the pasture and barn, and goats housed on pastures contaminated with Johne's disease will be moved to the dry-lot pens in Building 100. Goats housed on dry-lot pens have a much lower incidence of Johne's disease than those maintained on pasture. Additions to both wings of Building 100 are planned. They will provide additional dry-lot pens for housing offsprings of the Johne's-free goats.

Improvements will be made at Three Springs Farm because a decision to purchase it has been made. A temporary building to house poultry and a pole barn for sheep or goats will be erected. Additional farm fence will be installed.

The inventory of rhesus monkeys caught wild will be exhausted by the end of FY 1978 without further supplies. The primate quarantine unit has alternative plans, depending on the feral monkey supply. If no feral animals are received, the unit will phase in long-term research holding of nonhuman primates (including New World species), increase progeny holding to age animals for NIH intramural needs, and increase its collaborative research capability for defining animal models. If increased feral animals are received from Bangladesh or other sources, the unit will serve as a rhesus monkey quarantine and conditioning point for NIH and other government agency requirements, with progeny holding and research activities undertaken as space and manpower permit. If feral animals are received in reduced numbers, a portion of each of the above plans will be initiated.

Monkey breeding contractors are expected to provide 800 progeny by 1980. The estimated NIH requirement for small rhesus monkeys in FY 1979 is only 150 animals. Plans are therefore being made to modify the contracts to include holding facilities for rhesus monkeys until they are 3 to 4 years old and of desired weight.

2. Comparative Pathology Section

A program is being established, as outlined in NIH Manual Issuance 3043-1 "Introduction of Rodents and Rodent Products," to try to prevent introduction into NIH of rodents or rodent products infected with viruses of ectromelia or lymphocytic choriomeningitis.

The Central Institute for Experimental Animals, Japan, has requested that CPS assist in a program to standardize methods for genetic monitoring of inbred mice and methods for microbiologic monitoring of laboratory rodents, under the auspices of the International Council for Laboratory Animal Science. The genetic program has already entered into a collaborative association with the

Central Institute, which probably will continue in some form regardless of the degree of formality established. The microbiology program is giving consideration to the request. To become involved in such a program would require that a position for a serologist be made available. It is anticipated that the work would involve primarily the development and standardization of diagnostic reagents used in monitoring.

3. Small Animal Section

Renovations of Building 14E were completed and provide research and holding space for the Section's nutrition and animal health programs. The planning for renovation of the rodent facilities has been modified slightly. The requirement to house large expansion colonies from which to supply production contractors has diminished as a result of collaborative efforts with the National Cancer Institute. Nude mouse production will probably be expanded significantly in the coming year. When contracts are awarded for the production of noninbred mice and OM rats, a long-term holding capability will be developed for geriatric studies of rats.

Results of a management analysis survey indicated that computer applications would expedite animal maintenance and production programs as well as holding of research animals. Plans are being developed to apply and evaluate computer assistance in the proposed program for geriatric studies in rats.

It is anticipated that the genetics quality assurance program will be completed and become operational next year. A contract was awarded to provide guidance, through an expert committee, concerning additions to and deletions from the genetic resource. Utilization of the committee will be ongoing and is expected to result in the increased efficiency of space utilization in the resource. It is planned to initiate an embryo freezing and storage program to permit maintenance of potentially useful strains not currently in demand and an embryo "bank" for future use.

Contract specifications are being developed to update the NIH Rodent Catalogue and document the characteristics of strains and stocks maintained in the genetic resource. Documentation will be computerized to permit its use by the Laboratory Animal Data Bank of the National Library of Medicine.

Specifications have been developed for contract production of hamsters, OM rats, inbred guinea pigs, and NIH and general purpose mice. It is planned to advertise for contracts in the order listed as soon as funding becomes available for the renovation of Building 14F. Specifications were also submitted to obtain animal transportation services by contract instead of purchase order.

A review of commercially available caging for rabbits and guinea pigs was completed, and prototype caging was ordered for evaluation. Depending on the outcome, caging, with or without modifications, will be purchased during the next years. A new method of sterilizing animal drinking water for use in automatic systems will be evaluated. The method involves the use of silver ions.

4. Veterinary Medicine and Surgery Section

Collaborative and research support activities are expected to increase. The close interfacing of all three units in the Section aids in fulfilling the mission objectives of each. All will be affected by minor renovations.

Renovations of the facilities of the comparative medicine unit were delayed due to difficulties with the contractor. Plans to complete the renovations are being coordinated by the Division of Engineering Services. Some inconveniences will be experienced by BID investigators, but the unit's role in providing pre- and postoperative care will continue to expand.

The primate research unit plans to improve the ventilation system in Building 14D. Renovations and expansion of the surgery unit's facilities in Building 14E have been completed in large part, but numerous work requests (such as installation of a gas sterilization system, mounting of overhead surgical lights, and renovation of two radiographic rooms) must be fulfilled before the unit can be in full operation. Until then, BID investigators and VRB staff will have to tolerate inconveniences. Integration of space, equipment, supplies, and support personnel will permit effective use of the facility and allow reassignment of scattered smaller surgical areas to other BID research functions.

PUBLICATIONS

Baas, E.J., Trotter, S.L., Franklin, R.M., and Barile, M.F.: Epidemic caprine keratoconjunctivitis: Recovery of Mycoplasma conjunctivae and its possible role in pathogenesis. Infect. Immunol. 18: 806-815, 1977.

Clarke, G.L., and Osburn, B.I.: Transmissible congenital demyelinating encephalopathy of lambs. Vet. Pathol. 15: 68-82, 1978.

Hurley, L.S., Knapka, J.J., and Pleasants, J.R.: Nutrient Requirements of the Mouse. In Nutrient Requirements of Rodents and Fish Used in Biomedical Research. National Academy of Sciences, Washington, D. C. (In press.)

Morin, M.L., Renquist, D.M., Knapka, J., and Judge, F.J.: The effect of dietary crude fiber levels on rhesus monkeys during quarantine. Lab. Animal Sci. (In press.)

Renquist, D.M., Montrey, R.D., Hooks, J.E., and Manus, A.C.: Hematologic, biochemical, and physiologic indices of the sacred baboon (Papio hamadryas). Lab. Animal Sci. 27: 271-285, 1977.

Renquist, D.M., and Whitney, R.A.: Tuberculosis in Nonhuman Primates. Smithsonian Press (In press.)

Thomas, J.W., and Knapka, J.J.: Nutrient Requirements of the Gerbil. In Nutrient Requirements of Rodents and Fish Used in Biomedical Research. National Academy of Sciences, Washington, D. C. (In press.)

Thomas, J.W., and Knapka, J.J.: Nutrient Requirements of the Vole. In Nutrient Requirements of Rodents and Fish Used in Biomedical Research. National Academy of Sciences, Washington, D.C. (In press.)

Trotter, S.L., Franklin, R.M., Baas, E.J., and Barile, M.F.: Epidemic caprine keratoconjunctivitis: Experimentally induced disease with a pure culture of Mycoplasma conjunctivae. Infect. Immunol. 18: 816-822, 1977.

INDIVIDUAL INTRAMURAL PROJECT REPORTS

Biomedical Engineering and Instrumentation Branch

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10042-01 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)
The Use of Microprocessor-Based "Intelligent" Machines in Patient Care

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. Eden	Chief	BEIB DRS
OTHER:	H. Eden	Assistant to the Chief	BEIB DRS
	P. Bungay	Chemical Engineer	BEIB DRS
	W. Friauf	Chief	EEES BEIB DRS
	B. McLees	Chief	DCCM CC
	K. Kempner	Electronics Engineer	CSL DCRT
	R. Martino	Electronics Engineer	CSL DCRT
	R. Branson	Georgetown University	
	N. DeClaris	University of Maryland	
	T. Field	Franklin Pierce Law Center	
	M. Frankel	Wayne State University	
	C. Spiegel	George Washington University	
	A. Teich	Technoscience Associates	
	K. Warner	University of Michigan	

COOPERATING UNITS (if any)
DCCM-CC; CSL-DCRT; Georgetown University; University of Maryland; Franklin Pierce Law Center; Wayne State University; George Washington University; Technoscience Associates; University of Michigan

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES XX (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

As part of NIH's overall Consensus Development effort, BEIB is conducting a series of four open workshops on "The Use of Microprocessor-Based 'Intelligent' Machines in Patient Care." With techniques developed for technology assessment, a panel of NIH and non-NIH members of the academic community are attempting to reach consensus on social and technical issues underlying the development of systems capable of autonomously adjusting treatment of patients.

PHS-6040
(Rev. 10-76)

Objectives: To identify, clarify, and preliminarily assess the technical and social issues underlying the development of microprocessor-based "intelligent" machines for patient care -- especially as they relate to systems capable of autonomously adjusting treatment of patients.

Methods Employed: NIH and non-NIH members of the academic community are meeting in a series of four open workshops on the NIH campus in an attempt to reach a consensus on (1) the technology's current state-of-the-art, (2) its prospects for future development, and (3) a preliminary view of its potential, long-range, legal, ethical, social, medical, and economic implications.

Significance: The traditional, passive role that machines have played in the delivery of health care is being radically altered by recent developments in data processing, pattern recognition, and electronics microcircuitry. Machines capable of emulating intelligent behavior and making "judgments," independent of continuous physician supervision, may soon be developed for patient care; this study addresses the technological and social issues that such prospects raise.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10039-01 BEI

PERIOD COVERED
January 1, 1978 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Biophysical Instrumentation and Methodology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M.S. Lewis	Research Chemist	BEIB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Office of the Chief

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0.0

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The project is designed to develop new instrumentation and methodology or improve existing instrumentation and methodology for characterization of biological macromolecules. Analytical ultracentrifugation and techniques ancillary to it are the major areas of interest.

PHS-6040
(Rev. 10-76)

Objectives: To develop data acquisition systems for analytical ultracentrifuges and for ancillary equipment such as plate readers and densimeters and to develop appropriate software to use with the acquisition systems.

Methods Employed: We are reviewing methods used in development of other data acquisition systems and exploring the applicability of minicomputers and microprocessors to these problems. Plans for alternative systems are being made.

Significance: The development of suitable data acquisition systems should result in both quantitative and qualitative improvements in ultracentrifugal investigations. Data acquisition is presently the limiting factor in both of those aspects of such research.

Proposed Course: Decide on an optimum system or systems and implement that decision.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10040-01 BEI

PERIOD COVERED

January 1, 1978 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Physical Chemistry of Biological Macromolecules

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M.S. Lewis	Research Chemist	BEIB DRS
OTHER:	P. Davies	Research Associate	LMB NCI
	J.A. Gladner	Research Chemist	LCB NIAMDD
	S.I. Chung	Research Chemist	LB NIDR
	H. Shichi	Research Chemist	LVR NEI
	G. Chader	Section Head	LVR NEI
	J. Findlayson	Director	PDB BB
	D. Lui	Director	DBP BB

COOPERATING UNITS (if any)

None

LAB/BRANCH

Biomedical Engineering and Instrumentation

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DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.7	0.0

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to study the physical properties of a wide variety of biological macromolecules with the goal of correlating these properties to the structure and function of the macromolecules. The emphasis is on molecular size and shape, the thermodynamics of molecular interactions and molecular weight distributions. Analytical ultracentrifugation is the principal research technique used.

PHS-6040
(Rev. 10-76)

Objectives: To study the aggregation properties of filamin and the effects of proteolytic cleavage on them; to study the structure of lamprey fibrinogen by means of analyzing the size of the native molecule and constituent chains; to determine the molecular weight of the D fragment of human fibrinogen; to determine the molecular weight of retinol receptor sites in a semipurified retinal cytosol; to study the molecular weight and detergent-binding capacity of possible alternative forms of rhodopsin; to determine the molecular weight distributions of the A, B, and C polysaccharides of meningococcus.

Methods Employed: The various macromolecules have been isolated and purified from appropriate sources by conventional means. The molecular weights have been studied by equilibrium ultracentrifugation, and the resultant data has been analyzed by mathematical modeling techniques using the MLAB system on the DEC-10 computer.

Major Findings: Filamin, an actin-binding protein from smooth muscle and nonmuscle cells, has a monomer molecular weight of 250,000 in denaturing solvents and exists as a dimer with a small amount of high molecular weight aggregate in dilute buffers. In 0.6 M potassium chloride buffers, it appears to be in a reversible monomer-dimer equilibrium with various amounts of irreversible tetramer present, depending on the preparation and temperature maintained for the experiment. Cleavage with calcium-activated protease into light and heavy merofilamins with molecular weights of 10,000 and 240,000, respectively, abolishes all associating or aggregating properties.

Studies of lamprey fibrinogen suggest that it has an anomolous structure, with one large alpha chain and two beta and two gamma chains instead of the usual two of each kind. This postulate is supported by values for the molecular weight obtained ultracentrifugally in normal aqueous solvents and the molecular weights of the constituent chains in guanidine buffer obtained by Sepharose chromatography. The molecular weights of the chains in guanidine buffer obtained in the ultracentrifuge are in agreement with those values only when a significant change of the partial specific volume of the chains in guanidine is postulated. Initial studies on the whole fibrinogen molecule in guanidine buffer support our findings, but further work is needed for verification.

Disparate values for the molecular weight of the D fragment of human fibrinogen have been obtained by different investigators. The present study is attempting to resolve this by a series of experiments in normal buffers and denaturing solvent systems.

The molecular weight of retinol receptors from retinal cytosols has not been previously measured directly because it has not been possible to obtain sufficiently purified preparations of the receptors. In the present studies, this difficulty has been circumvented by determining the molecular weight from the ultracentrifugal distribution of the bound retinol, which was obtained by scanning at the wavelength of maximum absorption of the bound retinol. It was shown that only a single receptor species was present with a molecular weight of 16,000. Molecular weights estimated from other binding

studies are in good agreement with this value.

Two forms of rhodopsin complexed with digitonin have been isolated and studied in terms of their molecular weights and their bleaching and regeneration characteristics. The first form appears to be a complex of rhodopsin dimer with digitonin, bleaching slowly and regenerating rapidly; the second form appears to be a complex of rhodopsin monomer with digitonin and undergoes rapid bleaching and slow regeneration. Studies are presently directed toward more definitive elucidation of the nature of the rhodopsin-digitonin complexes and to examination of the possibility of a monomer-dimer transition in the bleaching-regeneration process.

Earlier ultracentrifuge data on the A, B, and C polysaccharides of meningococcus have been analyzed in order to obtain the molecular weight distributions of these polydisperse macromolecules. Weight-average and Z-average molecular weights for the entire cell contents, corrected for thermodynamic nonideality, have been used to calculate log-normal molecular weight distributions. The data are now being used to calculate other possible molecular weight distributions.

Significance: The studies on the molecular weight distributions for meningococcal polysaccharides are of practical importance for the development of vaccines against the bacteria since a direct correlations between the molecular weight of these polysaccharides and their immunogenicity has been demonstrated. The other studies are relevant to understanding of basic biochemical mechanisms involved in muscle, blood clotting, and vision. Additionally, the method developed for determination of the molecular weight of a receptor in a cytosol mixture has the potential of being applied to determination of the molecular weights of a wide variety of receptors that cannot be obtained in purified form, if appropriate chromophore-labeled ligands are developed.

Proposed Course: The studies on filamin have been completed, and a report is in preparation. The studies on fibrinogen are nearing completion and should be ready for publication shortly. The work on rhodopsin, receptor molecular weights, and polysaccharide molecular weight distributions will continue. Research to determine the extent of radiation-induced cleavage of proteins and polypeptides is planned.

Publications:

Wiggert, B., Bergsma, D., Lewis, M., Abe, T., and Chader, G.: Vitamin A receptors: Characteristics of retinol binding in chick retina and pigment epithelium. Biochem. Biophys. Acta 498: 366-374, 1977.

Wiggert, B., Bergsma, D., Lewis, M., and Chader, G.: Vitamin A receptors: Retinol binding in neural retina and pigment epithelium. J. Neurochem. 29: 947-954, 1977.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10001-10 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Pharmacokinetics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.L. Dedrick	Chief	ChES BEIB DRS
OTHER:	D.S. Zaharko	Pharmacologist	LCHPH NCI
	R.E. Jones	Mechanical Engineer	BEIB DRS
	A.M. Guarino	Chief	LT NCI
	R.J. Lutz	Chemical Engineer	BEIB DRS
	A.F. LeRoy	Chemical Engineer	BEIB DRS
	M.W. Anderson	Mathematician	BB NIEHS
	P.M. Bungay	Chemical Engineer	BEIB DRS
	H.B. Matthews	Pharmacologist	PB NIEHS
	I.G. Sipes	Assistant Professor	Univ. of Arizona
	C.E. Myers	Oncologist	CPB NCI
	J.M. Collins	Guest Worker	BEIB DRS

COOPERATING UNITS (if any)

LCHPH-NCI; PB-NIEHS; AK-CU Program NIAMDD; M-NCI; EB-NIEHS; CPB-NCI.

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
CRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	1.0

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☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Pharmacokinetic models are developed for the distribution and disposition of drugs, environmental contaminants, and endogenous metabolites in animals and man. They provide a plausible set of equations that can be used to extrapolate data from animals to man and thereby to improve chemotherapy, hemodialysis, and risk assessment.

PHS-6040
(Rev. 10-76)

Objectives: Improve and extend mathematical models for the distribution and disposition of drugs, environmental contaminants, and endogenous metabolites in animals and man to:

(1) Account for species differences in drug distribution.

(2) Provide rational bases for extrapolation of toxicity from animals to man.

(3) In conjunction with pharmacodynamics, provide a basis for optimization of cancer chemotherapy and chronic hemodialysis.

(4) Enable rational transfer of in vitro thermodynamic and kinetic data to in vivo cases.

(5) Predict effective dose schedules of anticancer drugs in individual patients with particular emphasis on intraperitoneal drug administration.

Methods Employed: Mathematical models are developed from physiocochemical, physiological, and anatomical information and the principles of chemical reaction engineering. Resulting sets of differential equations are solved analytically or numerically and compared with experimental data. Uncertainties are clarified by additional experiments and model modification.

Major Findings:
(1) Ovarian cancer is being treated by intraperitoneal administration of anticancer drugs according to pharmacokinetic principles. Preliminary results with methotrexate support our prediction of significant concentration differences between peritoneal fluid and plasma. Treatment of one patient with 5-fluorouracil (5-FU) has helped to define a nontoxic concentration range. Laboratory investigations and mathematical modeling are proceeding to refine our understanding of the pharmacokinetics and toxicology of 5-FU, adriamycin, and cis-dichlorodiammine platinum (II).

(2) Detailed transport studies of methotrexate in the Lewis lung tumor, gastrointestinal tract, and bone marrow of the mouse have shown that the resistance of this tumor may be explained on the basis of pharmacokinetic principles. Transport in all three tissues is facilitated and saturable; however, the permeability of the tumor is only one-half that of the gastrointestinal tract. The target enzyme, dehydrofolate reductase, has about ten times the concentration in the tumor as in the gastrointestinal tract.

(3) Work is proceeding on determination of the distribution and disposition of chlorinated biphenyls in the monkey and dog. The mathematical model developed previously for the rat will be applied to determine which parameters are predictable and which must be determined experimentally. That information should have fundamental importance to extrapolation of results from laboratory animals to man.

(4) A pharmacokinetic analysis was made of the exchange of Kepone between blood and gut contents across the gut wall. The analysis is based on three kinds of experiments in rats; (1) transport along the gastrointestinal tract of an orally administered, nonabsorbable tracer, (2) intravenous administration of Kepone to rats with bile ducts cannulated, and (3) oral administration of Kepone to intact rats. The model treats the intestine as a series of segments, each of which is subdivided into blood, tissue, and lumen subcompartments. The data were consistent with the assumption that Kepone exchange across the two interfaces (blood-tissue and tissue-lumen) is passive and diffusion-limited and can be characterized by symmetric permeability-area transport coefficients. According to this study, bile excretion is relatively unimportant for elimination of parent Kepone from the body. Rather, an equilibrium may be achieved between blood and feces with respect to the parent compound. Through use of the model, scaled up to man, it has been possible to estimate an upper limit to the augmentation of Kepone excretion achievable through use of orally administered, nonabsorbable adsorbents such as cholestyramine.

Significance: Drugs and other chemicals are tested for effect in animals, with the aim of extrapolating results to man. At issue are both the risk associated with environmental contaminants and optimization of therapy.

Proposed Course: Continued pharmacokinetic modeling with consideration of pharmacodynamic and cytokinetic events. Continued clinical emphasis through support of intraperitoneal procedures and other measures to overcome drug resistance. Increased emphasis on research designed to investigate distribution of environmental contaminants.

Publications:

Dedrick, R.L., Myers, C.E., Bungay, P.M., and DeVita, Jr., V.T.: Pharmacokinetic rationale for peritoneal drug administration in treatment of ovarian cancer. Cancer Treatment Rep. 62: 1-11, 1978.

Guarino, A., Anderson, J., Briley, P., Dedrick, R., English, B., Fenstermacher, P., Kinter, M., LeRoy, A., Owens, A., Rittmaster, R., and Sutermeister, K.: Pharmacokinetic studies of antineoplastic agents in the dogfish, Squalus acanthias. Bull. Mt. Desert Island Biol. Lab 15: 44-45, 1975.

Anderson, M.W., Eling, T.E., Lutz, R.J., Dedrick, R.L., and Matthews, H.B.: The construction of a pharmacokinetic model for the disposition of polychlorinated biphenyls in the rat. Clin. Pharmacol. Therap. 22: 765-772, 1977.

Jones, R.B., Myers, C.E., Guarino, A.M., Dedrick, R.L., Hubbard, S.M., and DeVita, Jr., V.T.: High-volume intraperitoneal chemotherapy ("Belly Bath") for ovarian cancer; pharmacologic basis and early results. Cancer Chemother. Pharmacol. (In press)

Collins, J.M.: Peritoneal dialysis for methyprylon intoxication. (Letter to the Editor) J. Pediatr. 92: 519-520, 1978.

Yang, K.H., Fung, W.P., Lutz, R.J., Dedrick, R.L., and Zaharko, D.S.: In vivo estimation of transport parameters characterizing the uptake of methotrexate by murine Lewis lung tumor. AphA Acad. Pharm. Sci. Abstracts 7: 129, 1977.

Dedrick, R.L., Lutz, R.J., Yang, K.H., Fung, W.P., and Zaharko, D.S.: Transport Studies of Methotrexate in Normal Tissue and the Lewis Lung Carcinoma. In Proceedings of the 70th Annual AIChE Meeting, New York, New York, 1977, Paper No. 43g.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10002-13 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Implant Device Development

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.W. Boretos	Physical Scientist	BEIB DRS
OTHER:	C.L. McIntosh	Senior Surgeon	SU NHLBI
	D.C. Syracuse	Clinical Associate	SU NHLBI
	W.S. Pierce	Associate Professor	Penn. State Univ.
	W. Derkac	Clinical Associate	SU NHLBI
	N. Iriguchi	Guest Worker	Asahi Chem. Co.
	J. Doppman	Radiologist	DR CC
	J. Wilkins	Physical Scientist	BEIB DRS

COOPERATING UNITS (if any)

SU-NHLBI: DR-CC: Pennsylvania State University, Asahi Chemical Company

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.7	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of the project is to elucidate the interaction of biomaterials used for specific implants with the physiological environment and to explore specially prepared materials and design features with respect to their suitability and performance in a variety of contexts. After removal from the host organism, implants will be examined for lipid absorption, protein deposition, changes in surface-free energy, and alteration of physical properties. Prostheses such as artificial hearts, heart valves, catheters, and electronic implants will be employed. Observations should include scanning electron microscopy (SEM), infrared spectroscopy, contact angle measurements, and energy dispersive X-ray analysis. Physical measurements will be made of tensile properties, flexural-fatigue resistance, electrical properties, hardness, density, coefficient of static and kinetic friction, hydrophilicity, and other surface and bulk properties.

PHS-6040
(Rev. 10-76)

Objectives: Elucidate the interaction of polymers, metals, and ceramics used for specific implants with the physiological environment; explore specially prepared polymers and design features with respect to their suitability and performance in a variety of contexts.

Methods Employed: Basic composition of the biomaterials is carefully controlled, and modifications are employed to enhance acceptability by the living system. After removal, implants are examined for lipid absorption, protein deposition, changes in surface-free energy, and alteration of physical properties. Observations include SEM, infrared spectroscopy, contact angle measurements, energy dispersive X-ray analysis, and atomic absorption spectroscopy. Flow characteristics and pressure gradients across heart valve implants are studied in vitro in a test apparatus. Electronic implants are examined periodically in vivo for changes in threshold levels, corrosion, and tissue reactivity. In vitro studies of the aforementioned are designed to accelerate fatigue testing and methods of improvement through heat treatment of the metal components undergoing stress. Surfaces of catheters are modified using surface treatments of grafted polymers and copolymers to reduce drag through the blood vessels. These catheters are tested for burst strength, stiffness, tensile strength, and density. The basic composition is modified through compounding. Embolizing agents consisting of composites of polymers, ceramics, and metals are being devised for delivery through the catheter systems so as to block arteries and vessels in the treatment of lesions such as aneurysms and arteriovenous malformations.

Major Findings: Tempering of cobalt chromium alloys at 710° F, when used for transthoracic pacemaker electrodes, has increased flexural fatigue resistance while maintaining adequate stiffness for insertion.

Some forms and compositions of embolizing agents implanted in cats and monkeys have proved to be unsatisfactory due to localized tissue reactivity.

Right pulmonary arterial heart assist balloon pumps of segmented polyurethane proved successful when implanted in a series of six sheep.

Miniaturized balloon catheters (i.e., less than 1 mm diameter) with a controlled drug delivery tip have been developed to reach malignancies heretofore inaccessible to drug treatment.

Significance: Physiologically compatible polymers with enduring strength are needed for such applications as heart valves, heart-assist devices, vascular implants, indwelling catheters, and subcutaneous uses.

Proposed Course: Extend experimental studies to further characterize the surface and bulk properties of biomaterials and, more specifically, determine their interactions with blood and subcutaneous tissue to facilitate development of better surgical implants.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10003-06 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Trace Element Analysis in Biological Materials

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A.F. LeRoy	Chemical Engineer	BEIB DRS
OTHER:	R.L. Dedrick	Chief	ChES BEIB DRS
	A.M. Guarino	Chief	LT NCI
	C.L. Litterst	Toxicologist	LT NCI
	T.E. Gram	Toxicologist	LT NCI
	S. Subramanian	Chemist	LMB NIAMDD
	R.J. Highet	Chemist	CH NHLBI
	D.A. Becker	Chemist	NBS
	H. Rook	Chief, Activation Analysis Section	NBS
	T. Gills	Chemist	NBS

COOPERATING UNITS (if any)

LT-NCI; LB-NCI; LNC-NIMH; LBS-NICHHD; National Bureau of Standards

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.6	0.4

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Flameless atomic absorption spectrophotometry and neutron activation analysis have been used for quantitation of platinum, magnesium, calcium, copper, zinc, iron, and some other elements in biological tissues and fluids. The analyses are important in biochemical, pharmacokinetic, and binding studies. Very sensitive analytical techniques are necessary because, in most instances, the elements are present in trace concentrations, and, in many cases, the sample size is very small as well. Separation techniques including ion-exchange chromatography, solvent extraction, and electrophoresis have been used to purify samples, fractionate and concentrate chemical species before analysis, and eliminate substances interfering with trace-level assays.

PHS-6040
(Rev. 10-76)

Objectives: The objective of this work is to improve analytical and identification techniques for metals in biological materials. Detection limits of the order of picograms to nanograms in milligram samples and simplified sample preparation have been sought. Quantitation of platinum, calcium, zinc, magnesium, and copper has been emphasized; other elements of biological significance are worked with as interest develops.

Methods Employed: Elemental analysis is being performed principally by flameless atomic absorption spectrophotometry. Control of temperatures generated in a graphite furnace as a function of time permits analysis even when considerable molecular and broad-band absorption occurs during combustion. Neutron activation analysis is being used to perform referee analyses.

Ion exchange chromatography and electrophoresis have been used to fractionate samples, with subsequent quantitation of metals in the fractions. With these techniques, improved resolution and analytical sensitivity are expected to permit findings of biological significance.

Major Findings: Ion exchange fractionation of platinum-containing chemical species in blood serum and urine and quantitation of the fractions have been performed to help in understanding the transformations that occur and their kinetics. The results obtained with urine from a patient treated with cis-dichlorodiammine platinum DDP, indicate the presence of three major species of closely related species. Operationally, these species are (1) "water-elutable," (2) "acid-elutable," and (3) irreversibly bound to the resin. In urine collected shortly after drug administration, the first predominates; the other two forms are negligible. With the progression of time, the water-elutable type diminishes, the acid-elutable form increases, and the resin bound form starts to appear. Preliminary results show that the first species diminishes at approximately the in vitro rate of hydrolysis of DDP. In vitro incubation of DDP with normal human urine shows development of the first two species but considerably less of the third. Studies of liver alcohol dehydrogenase indicate that it contains zinc with "structural" or "catalytic" function. Work is underway to improve the understanding of the role of zinc in the functioning of the enzyme.

Significance: Quantitation, identification, and characterization of metal species at trace levels in biological tissue samples, often very small, are important in biochemical research and environmental toxicology. Quantitation of a specific element in tissues and body fluids can aid understanding of drug action and other biochemical processes. Methods being developed offer quantitation of stable elements and obviate the need for radiolabeled substances in many instances.

Proposed Course: Extend applicability of direct combustion technique to include more tissue types. Try to minimize or eliminate pretreatment required. Complete analyses for pharmacokinetic modeling of the platinum compound, DDP. Perform necessary analyses for elements using neutron activation to confirm flameless atomic absorption spectrophotometry results. Expand use of chromatography to purify samples and fractionate and concentrate chemical species under study. 77

Publications:

Guarino, A., Anderson, J., Briley, P., Dedrick, R., English, B., Fenstermacher, P., Kinter, M., LeRoy, A., Owens, A., Rittmaster, R., and Sutermeister, K.: "Pharmacokinetic studies of antineoplastic agents in the dogfish, Squalus acanthias" Bull. Mt. Desert Island Biol. Lab. 15: 44-45, 1975.

LeRoy, A.F., Wehling, M.L., Sponseller, H.L., Friauf, W.S., Solomon, R.E., Dedrick, R.L., Litterst, C.L., Gram, T.E., Guarino, A.M., and Becker, D.A.: "Analysis of platinum in biological materials by flameless atomic absorption spectrophotometry." Biochemical Med. 18: 184-191, 1977.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 RS 10018-03 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Particulate Hydrodynamics in Porous Membranes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P.M. Bungay	Chemical Engineer	BEIB DRS
OTHER:	M.E. O'Neill	Visiting Scientist	BEIB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Mathematical models are being developed to describe passive membrane transport through pores or intracellular gap junctions. The Taylor-Aris dispersion analysis is extended to treat combined Brownian motion and convection in a single pore. The solute particle dimension is assumed to be large compared to that of the solvent molecules and also appreciable in size compared to the lateral pore dimension. The latter condition implies strong "hindered diffusion" and related solute-membrane interaction effects. A key aspect of the analysis is a generalized Einstein relation for predicting axial and radial components of the diffusivity tensor from hydrodynamics solutions for resistance coefficients. Perturbation techniques are used to obtain asymptotic solutions to the hydrodynamic equations, and the method of moments is employed to analyze the solute continuity equation.

PHS-6040
(Rev. 10-76)

Objectives: The objective of this project is to provide the basis for a rigorous, predictive continuum theory for passive transport phenomena in porous membranes, including such observations as "hindered diffusion".

Methods Employed: The essence of the approach is an extension of the Einstein continuum analysis for the Brownian motion of spherical molecules in dilute solutions. Einstein derived his predictive relation for the diffusion coefficient from the theoretical expression for the hydrodynamic resistance to translation of a rigid sphere through a homogeneous viscous fluid of infinite extent. The continuum analysis for porous membranes begins with a single solute molecule in a single pore and assumes that the form of Einstein's relationship between the diffusion and resistance coefficients remains valid. However, the presence of the rigid pore wall, in general, increases the hydrodynamic resistance to translation and rotation of the solute relative to the fluid. The diffusivity is thereby decreased in magnitude until, in the limit, as the solute dimension becomes equal to the lateral pore dimension, the diffusion coefficient falls to zero. Where there is, in addition to diffusion, net movement of the fluid through the pore, the hydrodynamic interaction similarly affects the solute flux relative to the solvent flux. The project is concerned with deriving the requisite expressions for the resistance coefficients from hydrodynamic theory as well as developing analyses for diffusive and convective porous membrane transport.

The primary theoretical tools used in the hydrodynamic problems are regular and singular perturbation techniques (typically using the ratio of solute to pore dimensions as the asymptotic expansion parameter) and collocation techniques of the type developed by Weinbaum and Pfeffer.

The transport analysis has been approached using the Taylor-Aris type dispersion treatment and the method of moments for deriving expressions for the pertinent coefficients without directly solving the complete solute continuity equation (convective-diffusion equation).

Major Findings: Progress has been made in modeling the transport of neutral spherical solutes through long slit-like pores with plane parallel boundaries. Electron micrograph evidence suggests that slit-like geometry is typical of the junctions between endothelial cells. The dispersion analysis developed in the previous reporting period has been refined by incorporating numerical evaluation of the Ho and Leal integral expressions for the resistance coefficients of the first order in the ratio of sphere radius to slit width.

For neutral spherical solutes in cylindrical pores, derivation and evaluation have been completed for correction to the resistance coefficients of the second order in the sphere-to-tube radius ratio. These results should lead to an improvement of the dispersion analysis of Gaydos and Brenner for convective and diffusive transport.

A derivation was completed for the asymptotic prediction of pressure drop versus flow in a cylindrical vessel with a constricted or dilated region.

Proposed Course: In addition to the models presently under study, it would be desirable to examine a situation in which the solute is a nonspherical body in order to determine how to handle particle orientation and rotational Brownian motion effects. An ellipsoidal solute would be the likely choice in terms of posing theoretically tractable problems. Another direction to pursue, which would greatly extend the range of applications for the theory, would be to incorporate into the present models nonhydrodynamic solute-membrane interactions such as electrostatic or London Van der Walls attractive/repulsive forces.

Significance: Channels (pores, slitlike gap junctions) represent one important type of transmembrane transport in biological systems. A rigorous conceptual and predictive framework for pore theory would be useful in clarifying relevant biological transport and would find wide applicability in engineering and physical science work pertaining to synthetic membranes.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10019-03 BEI

PERIOD COVERED

October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Instrumentation for Flow-Through Hollow Fiber Cell Culture Studies

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P.M. Bungay	Chemical Engineer	BEIB DRS
OTHER:	R.A. Knazek	Senior Investigator	LPP NCI

COOPERATING UNITS (if any)

LPP-NCI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Chemical Engineering

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.1	0.1

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☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

As part of studies aimed at improving the methodology for hollow fiber cell culture and investigating the response of cultured cells to pharmacologic agents, instrumentation systems are being developed for measuring relevant culture parameters. Instrumentation has been designed and built for monitoring the rate of oxygen consumption using a Clark-type amperometric oxygen electrode. Work on an electrode for monitoring the extracellular oxygen partial pressure is continuing. Subsequent parameters to be investigated are pH and carbon dioxide partial pressure.

PHS-6040
(Rev. 10-76)

Objectives: The short-range objective is to develop sensor and instrumentation packages for monitoring cell metabolism and growth parameters of cells being cultured in hollow fiber units. The long-range objectives are to (1) elucidate factors beneficial to maintaining and promoting growth and (2) determine the response of cells to pharmacologic agents.

Methods Employed: In the hollow fiber cell culture units employed in this study, the hollow fibers serve as semipermeable membrane barriers between the cultures outside the fibers and nutrient solution perfused through the fiber lumen. The fibers (typically 200 μm ID and 250 μm OD) permit exchange of oxygen, carbon dioxide, nutrients, products of metabolism, and other chemical substances ranging in size up to that of proteins like albumin. The fibers are packed roughly parallel and closely spaced such that diffusional distances typically do not exceed 100 μm. The fiber lumens are continuous with an external closed loop containing a nutrient solution and a pump to maintain recirculation of the solution through the pores. In some units two duplicate loops (hollow fiber bundle/reservoir/pump) are used; however, the two fiber bundles are braided together inside a single culture unit. The more complex systems are designed for studying convective as well as diffusive transport in the extracapillary space.

The effort thus far has been to develop the capability to measure (1) the rate of oxygen consumed by the cells in the unit and (2) the extracellular oxygen tension in the culture. Under steady conditions, the amount of oxygen given up by the nutrient solution in passing through the fibers is a measure of the rate of consumption by the cells. The connective tubing leading to the unit is of sufficient length so that the nutrient solution at the inlet to the culture unit is essentially saturated with respect to the carbon dioxide-enriched atmosphere. Measuring the difference in the partial pressure of the nutrient solution between the inlet and outlet of the culture unit permits calculation of the rate of delivery of oxygen to the cells using the medium flow rate and oxygen solubility. For this purpose an instrumentation package incorporating a Clark-type amperometric oxygen electrode has been assembled.

An electrode scheme for measuring the extracellular oxygen tension has been under development. The plan is to provide access for a fine wire electrode to the interior of a single nonporous, gas-permeable fiber in the bundle. The fiber will extend beyond both ends of the bundle and through the walls of the distribution caps covering the ends of the shell. Thus, the fiber will be bathed externally by the nutrient solution inside the caps, but will be exposed to the cell culture inside the shell. The fiber interior will be otherwise isolated and can be filled with a buffer solution appropriate to an electrode pair, such as platinum and silver/silver chloride.

Proposed Course: After satisfactory development of the oxygen monitoring systems, techniques will be examined for measuring other important cell culture parameters. Among the parameters to be looked at next are pH and carbon dioxide partial pressure in the extracellular fluid.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10041-01 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Flow Visualization Studies in Model Arteries

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.J. Lutz	Chemical Engineer	BEIB DRS
OTHER:	R.L. Dedrick	Chief	ChES BEIB DRS
	D.L. Fry	Chief	H IR OD

COOPERATING UNITS (if any)

OD - IR - NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

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Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

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0.5	0.3	0.2

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The appearance of atherosclerotic lesions at specific locations in the arterial tree has led many investigators to study the relevance of hemodynamic factors in atherogenesis. The purpose of this study is to investigate the patterns of flow in models of arterial geometries and to seek correlations between these flow patterns and the development of atherosclerotic plaques. In previous studies, quantitative measurements of the wall shear stress were made in model arteries by an electrochemical technique. However, the work provided no information about the direction of the shearing forces, and little idea about the nature of the flow patterns. In this study we will use various methods of flow visualization such as dye injection, hydrogen bubbles, and neutrally buoyant microsphere tracers to study the flow patterns in arterial models as a function of various flow parameters such as Reynolds number, branch flow ratios, and pulsatility. Both still photography and high-speed cinematography will record the flow phenomena. The work is in preliminary development stages, and various flow visualization techniques are being evaluated and refined.

Objectives: The objectives of this study are to visualize and record the various kinds of flow phenomena such as flow separation and secondary flow that may occur in complex flow channels that represent arterial geometry and to correlate the flow phenomena with the location of atherosclerotic plaques in experimental animals. The analysis will also include a quantitative measure of the velocity profiles at various sites in the model arteries.

Methods Employed: Several methods have already been shown to be useful for visualizing flow patterns in our model systems, and other methods will be tried. In the preliminary phases of this work, the following techniques have been used.

(1) Dye injection. At selected sites in the arterial model, small ports are drilled for insertion of #30 gauze hypodermic tubing, which is connected via PE 10 catheter tubing to a reservoir of colored dye. The end of the hypodermic tubing can be positioned at any radial location in the flow model and the dye slowly injected into the flow to mark the streamlines. The streamline patterns at several sites can then be recorded using 35-mm still photography. Initial data obtained by dye injection into the flow indicates that the flow streamlines are skewed toward the side-arm branches exiting from the main (aortic) flow channel and that unusual patterns of backflow and secondary flow occur near the channel wall just opposite the branch orifices.

(2) Hydrogen bubble technique. At selected sites in the arterial model, small grooves are milled into the model for the installation of 3-mil stainless steel wire. Several wires run across the diameter of the flow channel at locations in both the main branch and the side branches. The wires serve as cathodes in a system consisting of a remote anode and an electrolytic solution of sodium chloride. By pulsing a DC current through the system, hydrogen bubbles are evolved all along the cathode wire, which are in turn swept away by the flow. In such a manner, each element of fluid passing the wire is marked by the visible hydrogen bubbles and the shape of the velocity profiles can be recorded with appropriate photography.

(3) Neutrally buoyant microspheres. This method employs a dilute suspension of 100- to 500-micron diameter polystyrene microspheres in a 20 to 25 percent glycerine/water solution, which serves as the test fluid in the flow model. With proper illumination, the path of the microspheres can be photographed with high-speed cinematography as these neutrally buoyant particles move along with the fluid. In such a manner, the direction and velocity of fluid elements can be determined.

(4) Laser Doppler velocimetry. When light is scattered from a moving object, a stationary observer will see a change in the frequency of the scattered light (Doppler shift) proportional to the velocity of the object. This Doppler shift is used to measure the velocity of particles at various locations in the fluid. From the particle velocity, the fluid velocity is inferred. A laser is used as the light source because it is easily focused and coherent. This method allows us to determine, quantitatively, the velocity profiles at various positions in the arterial model.

Significance: Elucidation of the role of hemodynamics on the onset and development of atherosclerotic plaques is fundamental in the study of vascular disease. Certain biological evidence suggests that areas of increased plaque formation may correlate with areas frequently exposed to disturbed flow, for example, flow separation, or to relatively stable flow patterns that change direction and magnitude periodically throughout the day with varying metabolic and blood flow demands. This study should demonstrate various types of flow patterns that can occur in arterial systems as a function of changing flow parameters.

Proposed Course: (1) Design and fabricate arterial models. (2) Study the flow patterns in these models using the various techniques described above as a function of several flow parameters such as Reynolds number, branch flow ratio, and flow pulse frequency. (3) Correlate these findings with those of our previous experiments on wall shear stress in similar models. (4) Correlate all hemodynamic evidence with incidence of lesions in experimental animals.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10043-01 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)
Fiber Optic Probes/Oxygen Probes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.I. Peterson	Chemist	BEIB DRS
OTHER:	S.R. Goldstein	Mechanical Engineer	BEIB DRS
	R.M. Winslow	Senior Investigator	H IR MH

COOPERATING UNITS (if any)
H-IR-MH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Successful development of a fiber optic pH probe has provided a model for the extension of this approach to the construction of other probes, the most important being an oxygen probe. This requires the development of a suitable color indicator for oxygen, since none is available.

Objectives: Develop an oxygen sensor for tissue implantation to be used in studies of oxygen transport during exercise.

Methods Employed: A fiber optic measurement of dye-indicator response to oxygen.

Significance: In studies of abnormality in transport of oxygen to tissue by blood during exercise, measurements of oxygen pressure in the tissue can be used to determine the oxygen content of the blood supply via the blood oxygen saturation curve (concentration vs. pressure).

Major Findings and Proposed Course: The key ingredient for construction of a fiber optic oxygen sensor is a reversible color indicator for oxygen. Such is not available, but work in recent years on porphyrin compounds indicates that it should be possible to develop an oxygen indicator dye. Work is proceeding on the synthesis of a suitable compound.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10007-04 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)
Investigation of Oxidative Metabolism and Potassium Kinetics in the Cat Brain

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Chief	ACES BEIB DRS
OTHER:	B.A. Vern	Clinical Associate	CNB NINCDS
	W.C. Whitehouse	Electronics Technician	ADM CC
	N. Mutsuga	Visiting Fellow	CNB NINCDS

COOPERATING UNITS (if any)

CNB-NINCDS; AB-CC

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.0	1.0

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Oxidative metabolism, as indicated by the fluorescence of nicotinamide adenine dinucleotide (NADH) and oxygen consumption, was assessed to investigate potassium ion kinetics in the cat brain. Research was conducted to determine if the potassium clearance process is active or passive after activation of the cortex. Investigations were also conducted to determine the applicability of the NADH fluorescence technique to exposed myocardium. Active work on this project was completed before September 30, 1977; two papers were published subsequently.

PHS-6040
(Rev. 10-76)

Methods Employed: The NADH fluorescence at 470 nM is excited by illumination with ultraviolet light at 360 nM obtained from a high pressure Hg arc lamp. To compensate for blood volume changes within the field of interest, we developed and used a television fluorometer employing fluorescein dye as a reference. The technique, initially used for study of cat brain, was also applied successfully to exposed myocardium.

A potassium-sensitive microelectrode system was employed for measuring both extracellular and intravenous potassium ion levels.

Direct cortical oxygen consumption measurements were made by cannulation of the sagittal sinus and monitoring the flow rate and hemoglobin saturation of the blood flowing out of the sinus. The calculated oxygen consumption is proportional to the arterial-venous oxygen concentration difference multiplied by the flow rate.

For the Q_{10} experiments, the exposed cat hippocampus temperature was either elevated or lowered by use of a controlled temperature stream of artificial spinal fluid which flowed over the surface of the hippocampus. Surface temperature was monitored by a small thermistor probe.

Major Findings: The NADH dynamics observed in the myocardium are similar to those observed in the cortex.

Blood volume in transiently ischemic myocardial tissue may increase due to relaxed muscle tone.

Fluorescein fluorescence was found to be an excellent indicator of myocardial perfusion.

Agreement was found between an analytical model for potassium clearance and experimentally determined potassium kinetics. This agreement provided further evidence of the active clearance process previously suggested by Q_{10} measurements and the slowing of potassium clearance during periods of hypotension.

Publications:

Vern, B., Schuette, W., and Thibault, L: $\{K^+\}_o$ clearance in the cortex. A new analytical model. J. Neurophysiol. 40: 1015-1023, 1977.

Lewis, D.V., Mutsuga, N., Schuette, W.H., and Van Buren, J.: Potassium clearance and reactive gliosis in the alumina gel lesion. Epilepsia 18: 499-505, 1977.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10023-02 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Two-Dimensional Ultrasonic Imaging System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Chief	ACES BEIB DRS
OTHER:	W.S. Friauf	Chief	EEES BEIB DRS
	T.E. Hall	Electronic Engineer	BEIB DRS
	J.L. Doppman	Chief	DR CC
	T.H. Shawker	Clinical Associate	DR CC
	W.C. Whitehouse	Electronic Technician	ADM CC

COOPERATING UNITS (if any)
DR-CC; ADM-CC

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Several subsystems of a comprehensive, versatile, ultrasonic imaging and recording system have been developed. A second-generation real-time mechanical sector scanner has been put into use along with a video system for consolidation, displaying, and recording a variety of data. The development of a solid-state sector-to-TV scan converter is nearly completed. Work is continuing on a Doppler velocity measuring system designed to work in conjunction with the sector scanner. The overall system has proved to be especially useful in abdominal scanning and early detection of pregnancy.

PHS-6040
(Rev. 10-76)

Objectives: Development of a high-performance two-dimensional real-time ultrasonic imaging system with provision for Doppler velocity measurements at a selected point and standard TV output to facilitate video tape recording of an examination, including the sector, a view of the patient, real-time clock, additional alpha numeric information, moving trace ECG and pressure data, voice commentary, and audio and/or visual presentation of velocity data. Additional objectives are versatility, that is, suitability for ocular, cardiac, pediatric, and abdominal scanning with minor changes, and high benefit/cost ratio.

Rationale: To be suitable for cardiac usage, among others, a sector scan is virtually essential. While a phased array system is elegant, comparable results can be obtained by mechanically oscillating a single transducer through the desired scan angle. The latter approach has the following advantages: (a) the cost is much lower; (b) no degradation of beam pattern occurs near edges of scan; (c) the single ultrasonic element can easily be changed to provide a resonance frequency which is optimum for the problem at hand and (d) with only one transducer element, much more sophisticated duplexing, amplification, and signal detection can be achieved at reasonable cost.

Methods Employed: Based on the positive results obtained with the mechanical scanner designed and built earlier, a second-generation mechanical sector scanner was developed. The size of the scanner and mechanical vibration have been substantially reduced. In addition, the new scanner maintains electrical control of the scan pattern through the use of position feedback, which provides four major advantages relative to earlier mechanical scanners: (a) a simple control on the console permits the instantaneous change of scan width; (b) lines are spaced uniformly throughout the sector; (c) synchronization with standard TV systems is easy--a feature which facilitates high-quality imaging in video format; and (d) the instrument can be programmed to execute one or two scans per second, each requiring 1/15 second, with the scanner stopped at the center of the scan the remainder of the time to allow Doppler velocity measurements guided by the position information. Stopping the scanner most of the time is necessary to get a useful signal-to-noise ratio for the Doppler signal.

Major effort was directed to the development of a new device for converting the sector scan to video format. Digital storage in solid-state memory is being used, with conversion to and from analog voltages at the output and input, respectively. Compared to present scan converters, the solid-state unit provides a flicker-free display, thus facilitating concurrent spatial and velocity measurements as discussed above. Further, discrete scan lines are not imaged, and other image-processing or image-enhancing procedures can be readily incorporated. Reliability and ease of use should be greatly enhanced.

For the purpose of building up a TV picture with many types of information simultaneously for recording via video tape, appropriate commercial components have been assembled into a system.

Significance: The main significance is that, through suitable choice of approach, high-quality noninvasive visualization and recording can be achieved at a very reasonable cost.

Proposed Course: With the completion of the solid-state scan converter, a major effort will be made to improve image quality by adopting sophisticated techniques from other fields, such as radar and nuclear magnetic resonance, to the problem of using the same transducer for transmission and reception. Concurrently, attempts will be made to incorporate range-gated pulsed Doppler velocity measurement capability at a reasonable cost. Techniques that may eliminate the need for costly high-frequency power amplifiers and spectrum analyzers are also being explored.

Publications:

Shawker, T., Schuette, W., Whitehouse, W., and Rifka, S,: An Ultrasonic Real Time Sector Scanner for the Assessment of Early Fetal Development (Work in Progress). In Proceedings of the 2nd International Technology Transfer Workshop on Medical Diagnostic Ultrasound Imaging Technology, Cairo, Egypt, April 1977, 364-367.

Shawker, T., Schuette, W., and Whitehouse, W.: Real Time Sector Scanning of Common Abdominal Disease. In Proceedings of the 2nd International Technology Transfer Workshop on Medical Diagnostic Ultrasound Imaging Technology, Cairo, Egypt, April 1977, 259-368.

Schuette, W.H., Shawker, T.H., and Whitehouse, W.C.: Television synchronization or a real time ultrasonic sector scanner. J. Clin. Ultrasound 6: 1-72, 1978.

Schuette, W.H., Shawker, T.H., and Whitehouse, W.C.: An integrated television and real-time ultrasonic imaging system. J. Clin. Ultrasound 6: 271-272, 1978.

Friauf, W.S., Hall, T.E., and Bishop, R.: A Solid State Digital Scan Converter for an Ultrasonic Mechanical Sector Scanner. In Proceedings of the Association for the Advancement of Medical Instrumentation, March, 1978, 96.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10011-04 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)
Electrical Safety Program for Clinical Center Patients and Patient Care and Treatment Areas

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. Corsey	Electronic Engineer	BEIB DRS
OTHER:	W. Schuette	Chief	ACES BEIB DRS
	C. Strong	Environ. Service Officer	CC
	T. Johnson	Administrative Officer	CC
	J. Bucolo	Electronic Technician	BEIB DRS

COOPERATING UNITS (if any)

ADM-CC; SMS-BEIB

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0		1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An electrical safety program has been established to perform the following functions for the Clinical Center: establish electrical safety standards; test clinical electrical equipment; participate in the activities of the Clinical Center Safety Committee; train staff members regarding electrical shock and grounding; investigate electrical burns and shocks; survey the patient environment; provide counsel to medical nursing and administrative staff on purchase of new equipment; participate in the formulation of national electrical safety standards; design test equipment; modify existing clinical equipment to meet current safety standards.

PHS-6040
(Rev. 10-76)

Objectives: Establish and maintain a patient environment free of shock and burn hazard, assure that clinical equipment does not present an electrical hazard to patients, verify that clinical equipment and the patient environment are in compliance with the Joint Commission on Hospital Accreditation requirements, participate in the activities of the Clinical Center Safety Committee, provide input to the formulation of national electrical safety standards.

Major Findings: Standards for therapeutic electrical equipment are lacking. Instances of ungrounded equipment permitting high leakage of current have been discovered and corrected. Instances of unreliable electrical receptacles for life support equipment have been discovered. Unnecessarily expensive standards for inhalation anesthetics have been noted and corrected.

Significance: Health care facilities across the country now have reasonable standards for inhalation anesthetics, saving millions of dollars. The likelihood of shocks and burns in all areas has been reduced, and patients are no longer exposed to shock and burn hazards from most electrical equipment.

Proposed Course: Promote the establishment of a national standard for therapeutic electrical equipment.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10027-02 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Development of Whole-Body Hyperthermia Instrumentation and Control System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W.H. Schuette	Chief	ACES BEIB DRS
OTHER:	J. Bull	Senior Investigator	MC DCT NCI
	D. Lees	Staff Anesthesia	CC NIH
	J. Whang Peng	Senior Investigator	MS DCT NCI
	R. Corsey	Electronic Engineer	BEIB DRS
	H. Tipton	Mechanical Engineer	BEIB DRS

COOPERATING UNITS (if any)

MC-DCT-NCI; CC-NIH; MS-DCT-NIH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Whole body hyperthermia is being studied at NIH as a possible means of treatment for cancer. This project includes development of an instrumentation and control system based on utilization of a Tektronix 31 programmable calculator, digital plotter, and interface for data acquisition. The esophageal temperature of the patient is regulated to 0.1° C accuracy by feedback control of the temperature of water circulating in a set of hyperthermia blankets.

PHS-6040
(Rev. 10-76)

Methods Employed: A Tektronix 31 programmable calculator is being used to acquire, record, and process data as well as to control water temperature of a set of hyperthermia blankets. The temperature of the water pumped through the blankets together with esophageal and rectal temperatures of the patient are processed by the calculator, which then develops temperature commands for the water temperature mixing valve. The mixing valve adds hot or cold water to the flow stream returning from the blankets as directed by the calculator. A sixteen-channel analog multiplexer was designed to plug into the Tektronix digital interface unit so that heart rate, blood pressure, and temperature data could be processed by the system. The multiplexer module also provides commands from the calculator to the water mixing valve motor. Automatic cool-downs are programmed into the calculator in response to various out-of-limit conditions. The calculator functions in an interactive mode for entry of operational instructions.

Major Findings: The major finding from the use of the equipment is that it is possible to take the whole-body core temperature of patients to $42.0 \pm 0.1^{\circ}$ C for four hours on a biweekly basis without major difficulty. The finding suggests that hyperthermia treatment for cancer is practical. Currently, the system is being employed in conjunction with chemotherapy.

Publications:

Lees, D.E., Schuette, W.H., Whang-Peng, J., Bull, Joan M., Atkinson, E.R., and Macnamara, T.E.: Evaluation of Liquid Crystal Thermometry as a Screening Device for Elevations of Core Body Temperature. International Anesthesia Research Society, 52nd Congress, San Francisco, March 19-23, 1978 (Abstract).

Schuette, W.H., Atkinson, R., Bull, J.M.C., Corsey, R., and Lees, D.E.: Digital Control System for Whole Body Hyperthermia. AAMI 13th Annual Meeting, March 28, 1978. Washington, D.C. (Abstract), p. 133.

Bull, J.M., Lees, D.E., Schuette, W.H., Whang-Peng, J., Atkinson, E.R., Bynum, G., Smith, R., Gottdiener, J.S., Gralnick, H., and DeVita, V.T.: Whole Body Hyperthermia - Now a Feasible Addition to Cancer Treatment. In Proceedings of the Fourteenth Annual Meeting, AACR, Washington, D.C. 1978. (Abstract).

Meeker, W., Baskies, A., Lees, D., Bull, J., Peng, J., Atkinson, R., Schuette, W.H., and Cretien, Paul: Depressed T-Lymphocyte Levels with Response to Whole Body Hyperthermia (WBH) in Advanced Cancers. In Proceedings of the Fourteenth Annual Meeting, AACR, Washington, D.C. 1978.

Gottdiener, J.W., Bynum, G., Lees, D., Atkinson, R., Schuette, W.H., Peng, J., and Bull, J.M.: Hemodynamic effects of whole body hyperthermia in man. Clinical Res. 26: 235, 1978.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10021-03 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)
Development of an In Vivo Micro Spectrophotofluorometer for Use in Laboratory Animals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. Bonner	Physicist	BEIB DRS
	S.R. Goldstein	Mechanical Engineer	BEIB DRS
	P.M. Gullino	Chief	LPP NCI
	F.H. Grantham	Associate	LPP NCI
	R. Dedrick	Chief	CHES BEIB DRS
	L. Liotta	Physician	LPP NCI

COOPERATING UNITS (if any)

BEIB, DRS and LPP, NCI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering, Electrical Engineering, Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.7	1.0	0.7

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Technology and methodology has been developed to perform micro spectrophotofluorometry in caged laboratory animals using miniature fiber optic probes. The technique is being used initially for microwashout studies of tumors in rats using fluorescein injected intravenously to investigate variations in tissue perfusion in the tumors. In the next year, studies of tumor capillary permeability will be performed; measurements made with dextrans of varying molecular weight and labeled with fluorescein will be combined with analytical modeling. In the future, we hope to employ the technique to study metabolic behavior of tumors and pharmacokinetics of suitably fluorescent drugs in animals.

PHS-6040
(Rev. 10-76)

Objectives: (1) Develop the technology and methodology required to make in vivo fluorescence measurements in caged rats over a protracted period.

(2) Study the distribution and variation of local tissue perfusion in tumors implanted in rats.

(3) Investigate capillary permeability in tumors implanted in rats with and without intervention.

(4) Extend the technique to explore tissue metabolism under controlled conditions.

(5) Extend the technique to analyze in animals pharmacokinetics of drugs with inherent fluorescence.

Methods Employed: Pairs of single fiber optic strands are implanted along with tumor fragments in a rat and in its descending aorta. One fiber in each pair goes to a high-intensity light source; the other fiber of each pair goes to a multiplexed high-gain photomultiplier tube. Fluorescent dye injected into the cardiovascular system diffuses into the interstitial fluid of the tumor, is illuminated, fluoresces, and is eventually washed out. The time course of the fluorescence signal is then related to local tissue perfusion and other factors contributing to transport within the tumor. For permeability studies, dextrans of high molecular weight labeled with fluorescein will be used. The results will be compared with analytical models of the mass transport to determine permeability.

Major Findings: A new system based on the original test apparatus has been successful and is currently being used for studies in animals to determine regional tumor blood flow. A step-jump in measured arterial carboxy-fluorescein concentration gives an exponential increase in tissue fluorescence consistent with a flow-limited distribution of the fluorescence within the interstitial space of the tumor. Slower permeability-limited uptake of large molecular weight dextran has been observed. Fluorescein concentrations may be linearly monitored in situ over the range of 50 μM to 50 nM in tissue and 200 μM to 1 μM in blood with the present apparatus.

Significance: Development of this technique allows in vivo localized measurements in animals, not previously possible, on a long-term basis. A great variety of experiments involving blood flow, permeability, metabolism, and pharmacokinetics will become possible, which could enhance understanding of transport and metabolism in tumors and normal tissues.

Proposed Course:

(1) Complete the local tumor perfusion studies, begin the capillary permeability studies, investigate use of needle fluorescence probes for adriamycin pharmacokinetics.

(2) Carefully examine the light phenomena occurring in the tissue at the probe tip, complete the development of a computer interface for data processing, and extend use of device for related types of measurements by utilizing a laser light source.

(3) Investigate the possibility of performing metabolic studies and other fluorescence-related measurements.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10037-01 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Thermistor Digitizer

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T.R. Clem	Electronic Engineer	BEIB DRS
	C. Gibson	Electronic Engineer	BEIB DRS
OTHER:	R.L. Berger	Senior Investigator	LTD NHLBI
	G. Hemphill	Electronic Engineer	BEIB DRS
	W.S. Friauf	Electronic Engineer	BEIB DRS

COOPERATING UNITS (if any)

LTD NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.2	1.0	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A microprocessor-based instrument to measure temperature with a precision thermistor is being developed for general laboratory use as well as long-term evaluation of thermistor stability over a wide temperature range. Several operating modes allow sampling rate to be traded off against frequency of adjustment of thermistor power and automatic zeroing. Control of thermistor power will minimize self-heating errors.

PHS-6040
(Rev. 10-76)

Objectives: Develop an instrument with the following features:
1. Precise automatic control of thermistor excitation power despite wide fluctuations in thermistor resistance.
2. Accuracy and stability comparable to the best alternating current bridges but without the need for critical resistive and capacitive balancing.
3. Accurate linearization of the output over a 0 to 100° C temperature range.
4. High-speed digital data acquisition, processing, and storage.

Methods Employed: A microprocessor-based system allows control of excitation power on the basis of the measured resistance of the thermistor. The excitation is programmed to zero immediately before a measurement so that thermoelectric potentials and amplifier offsets can be compensated as with an alternating current bridge. Signal detection is affected by digital subtraction rather than by analog multiplication, providing higher accuracy and stability and freedom from capacitive balance problems. Linearization is performed digitally with high accuracy over a wide temperature range utilizing constants specific to the thermistor in use. Digital storage, display, and transfer of data are provided.

Significance: The system will permit easier and more accurate temperature measurement in a variety of analytical applications.

Proposed Course: Complete check-out of the system and refine performance until all specifications are met. Conduct accuracy and stability tests on system and thermistors. Apply to measurement problems.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10038-01 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Zeugmatography

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D.I. Hoult	Electronic Engineer	BEIB DRS
OTHER:	J.W. Hansen	Neonatologist	NPMB NICHD
	S.R. Goldstein	Mechanical Engineer	BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.1	1	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A nuclear magnetic resonance (NMR) imaging system is proposed for diagnostic studies, especially in babies. Zeugmatography provides an image of fluid collections and, therefore, could be useful in the diagnosis of conditions such as hydrocephalus, cystic malformations, intercranial bleeding, kidney malfunction, and congenital heart disease. A feasibility study has been completed, and the design of a suitable magnet and NMR spectrometer is now in progress. The magnet will employ windings on two hemispherical shells and consume about 5 kw of power. The spectrometer will operate at about 5 MHz and will employ a receiving coil and preamplifier with negative feedback in order to reduce the receiver dead time while not degrading sensitivity. The imaging method to be employed will depend on the experiment, but will normally be the rotating frame zeugmatography method developed in this laboratory.

PHS-6040
(Rev. 10-76)

Objectives: Explore the medical applications of zeugmatography, which is an imaging system that utilizes nuclear magnetic resonance (NMR) to detect fluid collections. Develop a zeugmatographic instrument to detect fluid-filled lesions in babies and limbs of adults.

Methods Employed: The technical difficulties involved in scaling zeugmatography experiments from normal NMR sample size (~5 mm) to adult human dimensions (~40 cm) are immense. Several laboratories are undertaking such a task in view of the possibly rich gains in the fields of cancer, cardiac, and metabolic research. Briefly, the problems involved in such scaling are lack of sensitivity (and thus resolution), excessive magnet power consumption, and receiver dead time following the pulse of radio frequency power required to stimulate the nuclei. If, however, the subject is a baby, the rewards, in terms of diagnosis of fluid-related conditions, are also rich, but the technical problems are less severe.

During the past nine months a feasibility study has been made of a magnet design and a new method of obtaining images. The study has indicated that the method may be applied with the consumption of modest amounts of power to obtain images with a resolution of the order of 1 mm in a 10-cm sample. The electrical design of a novel magnet built as two hemispherical shells has been completed, and the mechanical design is well underway. The problem of a receiver dead time has been solved, to a large extent, with the aid of negative feedback which dampens the ringing of the signal-receiving coil without introducing extra noise.

Significance: Possible applications of a small imaging system include the detection of fluid-filled cysts or dilations in the brain (hydrocephalus, cystic malformations, intercranial bleeding, etc.) abscesses, other fluid-filled cysts (kidney), and abnormal vasculature (congenital heart disease, atrioventricular malformations, etc.). Further, the instrument would be sufficiently large to accommodate adult extremities and thereby find use in the diagnosis of, for example, various arthritic conditions.

Proposed Course: Construct an NMR spectrometer suitable for imaging, fluid-filled lesions in babies. Evaluate the instrument, using animals as subjects.

Publications:

Lauterbur, P.C., "Image formation by induced local interactions: Examples employing nuclear magnetic resonance." Nature 242: 190, 1073.

Hoult, D.I., "Rotating Frame Zeugmatography," 19th Experimental N.M.R. Conference, Blacksburg, Va., 1978.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10015-03 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)
Development of Miniature Catheter for Clinical Use

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.R. Goldstein	Mechanical Engineer	BEIB DRS
OTHER:	J.L. Doppman	Chief	DR CC
	J.W. Boretos	Physical Scientist	BEIB DRS
	R. Jones	Engineering Technician	BEIB DRS

COOPERATING UNITS (if any)
DR-CC, ChES-MES-BEIB

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	.5	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A miniature topographic catheter attached to the end of a 1-mm #6 French catheter has been developed for insertion in tortuous blood vessels as small as 1 mm in diameter and up to 30 cm long. Techniques of delivering embolizing materials will be developed so that some procedures previously requiring surgery can be performed instead with catheters. Tests in animals will be performed next year.

PHS-6040
(Rev. 10-76)

Objectives: Develop techniques and devices for inserting a miniature catheter into small tortuous vessels.

Develop techniques and devices for delivering therapeutic materials into the catheterized vessel.

Major Findings: A miniature topographic catheter capable of negotiating tortuous paths in vitro has been sucessfully developed.

Significance: Surgeons and radiologists have long sought techniques for catheterizing small diameter vessels separated from larger, easily catheterized vessels by long, narrow passages with numerous bifurcations. The capability would permit selective treatment of tumors, aneurysms, and other lesions with minimal danger to normal tissues.

Proposed Course: Perform tests in animals and complete any indicated developmental work on the topographic catheter. Develop related devices and improved materials for embolization.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 RS 10022-02 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Fiber Optic Probes/pH Probe

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.R. Goldstein	Mechanical Engineer	BEIB DRS
OTHER:	J.I. Peterson	Chemist	BEIB DRS
	R.M. Winslow	Senior Investigator	H IR MH

COOPERATING UNITS (if any)

H-IR-MH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering and Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.7	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In the initial year of the project, a miniature pH sensor, based on fiber optics, was designed to pass through a 22-gauge needle intended for implantation in tissue for physiological studies during exercise. The operation of the probe depends on pH changes identified by dye indicators. The probe is connected to laboratory optical instrumentation.

During the past year, an electro-optic measuring and readout system was designed and developed specifically for the pH sensors. The new unit makes the overall system portable, practical, and easy to use. In vitro tests were performed to characterize the pH sensor and the instrument. In vivo tests in laboratory animals will be performed in the current year.

PHS-6040
(Rev. 10-76)

Objectives: Develop a pH sensor for tissue implantation to be used in studies of oxygen transport during exercise.

Methods Employed: A fiber optic measurement of dye indicator response to pH.

Significance: In studies of abnormality in transport of oxygen to tissue by blood during exercise, measurements of oxygen pressure in the tissue can be used to determine the oxygen content of the blood supply via the blood oxygen saturation curve (concentration vs. pressure). Alternately, measurements of the blood oxygen concentration can be used to determine oxygen pressure by this curve. Since the relation between oxygen pressure and concentration is affected by changes in pH which occur during exercise (shift in the curve with pH, the Bohr effect), it is necessary to incorporate a pH measurement with the oxygen measurement in making use of the curve.

Major Findings and Proposed Course: The electro-optic measuring and readout system for the fiber optic pH sensor has been developed and tested and works successfully. In vitro tests of the overall system indicate the following:

a) A precision (standard deviation) of 0.01 pH units over the range of interest of pH 7 to 7.4, after a calibration at 2 pH points

b) A temperature coefficient of 0.02 pH units per degree centigrade

c) An ionic strength coefficient of 0.01 pH units per 8 percent change in ionic strength at 37°C

d) A response time of 0.7 minutes (63 percent) to a step change in pH.

These characteristics should be sufficient for the proposed use. Further testing must be done to evaluate in vivo characteristics and suitability of the probe.

Publications:

Goldstein, Seth and Peterson, John I.: A Miniature Fiber Optic pH Sensor for In-Vivo Application. In Grood, E. and Smith, C. (Eds.): 1977 Advances in Bioengineering, New York, 1977, pp. 81-82, American Society of Mechanical Engineers.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10031-02 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Multimode Visual Display

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.B. Leighton	Mechanical Engineer	BEIB DRS
OTHER:	D. Reingold	Research Associate (IPA)	CB NEI

COOPERATING UNITS (if any)

None

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.3	0.7

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A servo-controlled, two-axis visual target projector, rotating optokinetic panoramic display, and integrated spherical projection screen have been developed. The system has been assembled, and final checkout is underway. The system will permit studies of visual tracking functions and visual-vestibular interactions.

PHS-6040
(Rev. 10-76)

Objectives: (1) To facilitate experiments concerned with control of eye movements and visual functions. (2) To permit experiments to be made with healthy human beings and patients with a variety of neurological disorders. (3) To permit precise and convenient measurements under computer control of visual and visual-vestibular interaction.

Methods Employed: The patient will be seated with his head at the center of a six-foot diameter spherical projection screen. A wide-angle lens and a projector system placed above the sphere provide a panoramic display on the interior surface of the sphere; a motor-driven slide in the projection system can create a rotating display. A separate projection system just above the patient's head consists of a long focal length optical device and a mirror pivoted about two axes. The mirror is driven by two high-performance direct current servomotors controlled by the computer. The second projection system will permit a small target to be moved (up to 2^{o}) rapidly on the screen to study visual tracking by the subject. A variety of slides can automatically be put in position in either projection system. Eventually the orientation or tilt of these images will also be under computer control.

Major Findings: The major parts of the system have been built and are currently being checked out.

Significance: The instrument will allow investigators in the National Eye Institute to conduct a variety of experiments on visual and visual-vestibular interactions. The position and velocity of various moving spots of light will be programmable, and experimental paradigms can be stored on a computer and called up when required.

Proposed Course: After the system is thoroughly checked out, this project will end. Further use of the device will be considered by NEI investigators.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 RS 10033-01 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Micropipette Pressure Transducer

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.B. Leighton	Mechanical Engineer	BEIB DRS
OTHER:	D.L. Fry	Physiologist	NHLBI

COOPERATING UNITS (if any)

NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.3	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A pressure transducer with a micropipette tip, 10 μ in diameter, and infinite direct current input impedance, is being developed.

PHS-6040
(Rev. 10-76)

Objectives: To be able to measure pressure gradients within arterial walls, or within other spaces where a tiny probe of infinite static fluid stiffness is required.

Methods Employed: A servo-balance design, utilizing a primary and secondary transducer and a piezoelectric actuator for balancing, is being employed. Accurate temperature control will also be maintained.

Major Findings: The device has been designed and is being constructed.

Significance: This device should be useful for research in atherosclerosis, and other studies in which intra- or intercellular fluid pressure is an important factor.

Proposed Course: After construction, the system will be thoroughly tested in vitro.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10034-01 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Three-Dimensional Histological Reconstruction

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: S.B. Leighton Mechanical Engineer BEIB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.3	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES XX (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A semi-automatic system for acquisition of three-dimensional structural information about histological material is being developed. The system should have significant speed and reliability advantages over present techniques using serial sections, although resolution may be limited. In brief, an embedded tissue block will be fixed relative to a scanning-electron-microscope imaging system, the surface of the block will be imaged and stored, and successive slices will be removed by a built-in microtome. Handling and registration of thin sections will thus be eliminated. Human and computer pattern recognition will transform the resulting set of images into a three-dimensional reconstruction.

PHS-6040
(Rev. 10-76)

Objectives: (1) To facilitate making schematic diagrams of neural nets. (2) To facilitate developmental studies of small organs and organisms.

Methods Employed: Various cutting, staining, and imaging techniques are being evaluated for best resolution.

Major Findings: So far, the feasibility of the project has been demonstrated, and resolutions to 600 Angstroms have been achieved in neural tissue.

Significance: Neuroanatomists may be able to trace significant neural nets easily enough to do enough samples to be statistically significant.

Proposed Course: Further optimization of cutting and etching will be done, followed by design and construction of a complete device.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10035-01 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Counter-Current Chromatography Without Rotating Seals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.B. Leighton	Mechanical Engineer	BEIB DRS
OTHER:	I. Ito	Visiting Scientist	LTD NHLBI

COOPERATING UNITS (if any)

LTD-NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.4	0.1	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES XX ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An improved mechanical design has been developed for a rotating counter-current chromatographic system without rotating seals. The design permits reliable operation in centrifugal fields up to 165 g, with independent control of spiral column rotation with respect to the field.

Objectives: To permit reliable, effective liquid-liquid counter-current separations without any rotating fluid seals.

Methods Employed: A double, epicyclic gear train is used to permit independently controlled speeds, a compact, stable structure, and topology within the constraints of the no rotating seals concept.

Major Findings: The instrument is complete and is under test.

Significance: The device will allow the laboratory of technical development, NHLBI, to pursue further studies in liquid-liquid chromatography.

Proposed Course: The instrument will be tested and delivered to NHLBI.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10036-01 BEI

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Endoscope Introduction

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S.B. Leighton	Mechanical Engineer	BEIB DRS
OTHER:	L. Bernstein	Internal Medicine	NLM

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.2	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A new technique for the introduction of endoscopes or catheters is being developed further. It makes use of the everting tube concept patented by Zeimar in 1970.

Objectives: To facilitate endoscopic examination and operation.

Methods Employed: New materials (urethane) and lubricants are being used to extend the concept of the original patent and permit practical application.

Major Findings: Urethane is a practical material for the proposed instrument, but wall thickness and durometer value must be closely controlled. Precise mechanical design will be required.

Significance: The difficulty of introducing endoscopic instruments is a significant impediment to their greater use. If this device can reduce that difficulty, the applicability of endoscopic examinations may be extended.

Proposed Course: Contingent on funding, further prototypes will be designed and tested, scaling up to a full-size, clinically useful instrument.

INDIVIDUAL INTRAMURAL PROJECT REPORTS

Veterinary Resources Branch

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS-00001-08 VR

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Animal Model Development

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: C. T. Hansen Geneticist VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Small Animal Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Md 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The program is concerned with developing animal models for biomedical research utilizing the VRB genetics resource by following the appropriate mating techniques. One component of the program involves forming, all on the same genetic background, four groups of mice which are defined with respect to T and B lymphocyte activity utilizing two independently occurring mutations; Nude (nu) which results in thymic dysgenesis and an X linked mutation which affects the maturation of B lymphocytes. This system is being established in 10 inbred mouse strains. Also, the mutant called Motheaten (me) is being established in four inbred strains of mice and the gene named Dwarf (dw) in three strains. In the rats, the gene Corpulent (cp) is being established in two strains and the genes Diabetes Insipidus (di) and Jaundice (j) in two strains.

Objectives: To develop animal models for biomedical research.

Methods Employed : Application of the appropriate mating system in combination with continuous physiological monitoring to yield the desired model.

Major Findings: The progress in developing the immunologically defined mice continues to be satisfactory. At least three to five years will be required to complete the developmental program although a pilot program utilizing this system in the N:NIH(S)-nu/nu outbred stock has reached the stage where animals are now being used in a number of research programs. Preliminary results suggest that these may yield a powerful tool in areas such as infectious diseases, oncology and parsitology. The remainder of the breeding programs also are progressing. It is anticipated that within the year, genetically defined rats carrying the gene Diabetes Insipidus (di) will be available for research. One research program using genetically defined rats carrying the Jaundice (j) gene has been undertaken.

PROJECT NUMBER (Do NOT use this space)	HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00002-07 VR

PERIOD COVERED

October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Development of Diets for Laboratory Animals

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI	:	J. J. Knapka	Nutritionist	VRB DRS
OTHER:	:	K. P. Smith	Geneticist	VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH

Veterinary Resources Branch

SECTION

Small Animal Section

INSTITUTE AND LOCATION

Division of Research Services, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	0.5	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A laboratory animal nutritional research program is being conducted with various strains and stocks of small animals maintained in conventional and specific pathogen-free environments. The primary objectives of the program are to develop and evaluate rations that can be used to improve the nutritional status of animal colonies and to identify differences in nutrient requirements among various strains and stocks of animals. A series of factorial-designed feeding trials are conducted to determine the effect of varying concentrations of major and minor nutrients on growth, reproduction, and maintenance of different rat, mouse, guinea pig, and rabbit strains.

PHS-6040
(Rev. 10-76)

Objectives: To improve the nutritional status of NIH production colonies of laboratory animals by identifying the quantitative nutrient requirements of specific stocks and strains of animals and then developing open-formula rations (that is, rations with ingredients completely listed) that contain these nutrient concentrations. To identify possible differences in nutrient requirements between animals maintained in conventional and specific pathogen-free environments. To provide NIH investigators with open-formula rations to accommodate specific research projects.

Methods Employed: A series of factorial designed feeding trials are conducted to determine the effect of varying dietary concentrations of crude protein, crude fat, crude fiber, minerals, and vitamins on growth reproduction in mice, rats, guinea pigs, and rabbits maintained in conventional and specific pathogen-free environments. Criteria of evaluation include number of pregnancies, number of litters born and weaned, number of pups born and weaned, mortality, weight of offspring weaned, and the post-weaning growth of offspring. Studies are also being conducted to determine the digestibility of nutrients in experimental rations. Data from all studies are coded for computer analysis.

Major Findings: The continued evaluation of production records from foundation mouse and rat colonies indicate the level of reproductive performance has been maintained during the two years these colonies have been fed an open formula diet containing 18 percent crude protein instead of a 24 percent crude protein commercial diet. The Data collected from the three successive generations of animals fed a new diet is generally required to show that a given dietary nutrient concentration will have no latent effect on future generations.

Studies with inbred guinea pig colonies show that the increased neonatal mortality rates which occurred after a new NIH open formula diet was introducted in the colonies was a result of the dietary change but was not caused by the new diet per se.

A new series of special rations have been developed for studies designed to determine the effect of various kinds of dietary fat and cholesterol on the distribution of atherosclerosis in dogs and miniature swine. Results from these studies indicate the cause of this disease can be altered by dietary alterations.

Significance: The efficiency of production and research colonies of laboratory animals can be markedly improved when rations supply nutrients in concentrations nearly equal to the requirements of the animal strain involved. Open-formula rations developed for specific research projects, or for standard rations, provide NIH investigators and the scientific community with an essential research tool when experimental data is to be verified by repeated experiments.

Proposed Course: Continuation.

PROJECT NUMBER (Do NOT use this space)	HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00004-17 VR

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Tyzzer's Disease

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.R. Ganaway	Veterinary Microbiologist	CPS VRB DRS
OTHER:	T.H. Spencer	Microbiologist	CPS VRB DRS
	A.M. Allen	Chief, CPS	CPS VRB DRS
	G.L. Clarke	Veterinary Pathologist	CPS VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☒ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The continuing purpose of this project is the study of Tyzzer's disease. The topics of present interest are: (1) characterization of the causative agent, Bacillus piliformis; (2) the serological response of the host to B. piliformis infection using the complement fixation test and fluorescent antibody techniques; (3) the relationship of isolants from the rabbit and horse foal; (4) the pathogenesis of Tyzzer's disease in a variety of laboratory animals; (5) the stability of the spores of B. piliformis under a variety of conditions including temperature variation and contact with chemicals; and (6) the epidemiology of Tyzzer's disease, the goal being to identify primary sources of the infection.

Objectives: To further characterize the etiologic agent of Tyzzer's disease. To study the pathogenesis of the disease through experimental transmission studies. To develop serologic techniques for detection of antibody. To develop means to prevent or control the disease.

Methods Employed: Microbiology, immunology, and pathology.

Major Findings: Vesphene, Zephiran Chloride, Microquat, Wescodyne, formalin and peracetic acid, chemical compounds commonly used to sanitize or disinfect surfaces in various types of animal quarters, were tested for sporicidal effect on the spores of B. piliformis. The only compounds found to be effective, clorox and peracetic acid, are not normally used in conventional animal quarters where Tyzzer's disease most commonly occurs. The most commonly used chemicals in these areas (quaternary ammonium, phenolic, and aqueous iodine types) appear to be ineffective against B. piliformis spores of rabbit origin.

Significance: Often occurring as an epizootic, Tyzzer's disease causes fatal disease in mice, rats, hamsters, gerbils, laboratory rabbits, guinea pigs, nonhuman primates, cats, dogs, horses, wild hares, cottontail rabbits, coyotes, and muskrats. The etiologic agent, a Gram-negative, spore-forming, obligate intracellular parasite, is unique in the field of microbiology and remains unclassified. The disease occurs throughout the world and is one of the more important diseases of laboratory animals that interferes with and complicates biomedical research.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 RS 00008-04 VR

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Neoplasia in the Nude Mouse

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. L. Clarke	Veterinary Pathologist	CPS VRB DRS
OTHER:	C. T. Hansen	Geneticist	SAS VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.2	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Tumors involving many organ systems have been collected from the nude mouse, which has a genetic deficiency in cell-mediated immunity. They are being classified histologically. The information is being correlated with nude mouse production figures to assess the incidence of neoplasia in the nude mouse and determine if there is a relationship between the genetic deficiency and the incidence of tumors.

PHS-6040
(Rev. 10-76)

Objectives: To determine the incidence and types of neoplasia that occur in the nude mouse, an inbred strain genetically deficient in cell-mediated immunity.

Methods Employed: Retired females are maintained behind the barrier in Building 14G for aging and sent to the Comparative Pathology Section when they show signs of abnormality. Males are sent to the Section following retirement and are maintained in relative isolation and killed when they exhibit abnormal signs.

Major Findings: Neoplasms collected to date are being studied by light and, in exceptional cases, electron microscopic methods.

Significance: Determination of whether nude mice have a significant rate of neoplastic disease will be a worthwhile contribution to evaluating the relationship between cell-mediated immunity and neoplasia.

Proposed Course: When all collected neoplasms have been classified, the data will be prepared for publication.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-RS-00009-05 VR

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Sodium Cyanate Neurotoxicity in Macaca nemastrina Primates

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. K. Johnson	Chief, VMSS	VRB DRS
	R. A. Whitney, Jr.	Chief	VRB DRS
	F. Anderson	Chief, MH	IR NHLBI

COOPERATING UNITS (if any)

Molecular Hematology Branch, Division of Intramural Research, NHLBI

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.6	0.3	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Sodium cyanate, a chemotherapeutic agent for sickle cell disease, inhibits irreversibility of the sickling of erythrocytes from patients with the disease by reacting specifically with the NH_2-terminal valine of the hemaglobin molecule without significantly destroying metabolism or function. We are studying whether sodium elicits neuropathologic lesions in pig-tailed monkeys, Macaca nemastrina, as has been suggested. The outcome of this study will provide information for development of clinical studies of human beings with sickle cell disease.

PHS-6040
(Rev. 10-76)

Objectives: This study will evaluate the neurotoxicity of sodium cyanate in pig-tailed monkeys with emphasis in the peripheral nerves. The degree of safety of this drug will help to determine whether its use should be given directly to patients or used with extracorporeal medical devices.

Methods Employed: Twenty adult female pig-tailed monkeys (Macaca nemastrina) were divided into four groups: one served as a control and the other three groups received daily subcutaneous injections of sodium cyanate in amounts of 35, 25, or 15 mg per kilogram. Neurological examinations and laboratory tests were conducted initially, during the course of the drug trial, and over a three-month stabilization period. Selected animals were humanely killed and perfused for neuropathological examination.

Major Findings: Animals receiving 35 mg or 25 mg per kilogram exhibited impaired propioceptor peripheral nerve reflexes and intermittent anorexia. The signs were more apparent in the 35-mg group. These animals had demyelination of both pyramidal tracts in the spinal cord. The lesion was characterized by distention of the myelin sheaths, leaving detached axys cylinder. Some of the myelin sheaths appeared confluent, with other distorted sheaths forming large intramyelinic spaces. A few scattered fibers indicated remyelinating activity. The peripheral nerves showed no abnormalities except for an occassional dense, swollen axon. The animals treated with 15 mg per kilogram did not have lesions nor clinical illness.

Significance: Sodium cyanate reverses the sickling of erythrocytes and results in relief of symptoms of sickle cell disease without impairing the oxygen transport system of erythrocytes. Establishing a dose-toxic curve in primates will lead to development of safe clinical dosage curves for human beings with the disease. Sodium cyanate is of interest for in vivo clinical use as well as extracorporeal treatment of affected erythrocytes. The drug has potential for treatment of other anemias associated with abnormal hemoglobin caused by genetic errors of metabolism.

Proposed Course: Project completed.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-RS-00011-04 VR

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Effect of Season on Pituitary and Gonadal Hormone Levels in Adult Male Macaques

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. K. Johnson	Chief, VMSS	VRB DRS
	G. D. Hodgen	Chief, ES	RR NICHHD

COOPERATING UNITS (if any)

Section on Endocrinology, Reproduction Research Branch, NICHHD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.25	.25	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this study is to assess the seasonal changes in endocrine parameters important in male fertility. Measurements of androgens measured as a biorhythm will be correlated to breeding efficiency and season.

PHS-6040
(Rev. 10-76)

Objectives: In most studies of infertility, the major emphasis of investigation is on the female. This study encompasses a longitudinal analyses of fertility in the male rhesus monkey, Macaca mulatta, to investigate cyclic patterns of spermatogenesis.

Methods Employed: Ten male breeder monkeys were bled the first five days of each month for a 12-month period. Follicle-stimulating hormone, luteinizing hormone, testosterone, and androsterone were assayed, using sensitive radioimmunoassay methods. The results were correlated with time of month, season, and breeding efficiency. Currently, radioisotope analyses of serum are being repeated.

Significance: Fertility and sterility studies focusing on male endocrine parameters have not been extensive. Approaching male endocrine changes as a biorhythm may lead to basic understanding of reproductive endocrinology. In addition, our results may be applied directly to biomedical research to improve nonhuman primate breeding, which is important because large-scale domestic colonies are a major resource to the scientific community.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-RS-00012-04 VR

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Hormone Levels During the Postpartum Interval in Nursing and Nonnursing Macaques

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. K. Johnson	Chief, VMSS	VRB DRS
	G. D. Hodgen	Chief, ES	RR NICHHD

COOPERATING UNITS (if any)

Section on Endocrinology, Reproduction Research Branch, NICHHD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	.05	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The interval from delivery to the first fertile menstrual cycle in rhesus monkeys (Macaca mulatta) is not known. Breeding management requires such information to maximize the use of breeder males for space management planning and efficiency in timed-mating protocols. Serum levels of various gonadal hormones will be measured to identify the onset of ovulating menstrual cycles.

Objectives: The most effective contraceptive mechanism among women in developing countries is lactation. The birth time interval is directly related to the lactation period in nursing mothers. This study will use the rhesus monkey as a model to examine endocrinological mechanisms influencing the onset of ovulation after birth.

Methods Employed: Five nursing rhesus monkey mothers and five nonnursing mothers will be bled for 90 days beginning one day after delivery. Serum levels of follicle-stimulating hormone, leutinizing hormone, estradiol, estrone, and progesterone will be measured to identify the onset of ovulatory menstrual cycles.

Major Findings: Analyses of serum hormones are not completed due to changes in techniques.

Significance: Development of domestic breeding colonies of rhesus monkeys for biomedical research requires better understanding of their reproductive physiology leading to improved fertility and management practices. Our results may also provide endocrine parameters applicable to studies of human beings.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00014-04 VR

PERIOD COVERED
October 1, 1977, to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Evaluation of Efficacy of M. bovis PPD Tuberculin in the Detection of Tuberculosis in Wild Caught Indian Rhesus Monkeys

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	D.M. Renquist	Head, PQU	VRB DRS
OTHER:	M.L. Morin	Veterinarian	VRB DRS
	D.W. Johnson	Clinical Veterinarian	U of Minn
	L. Conyha	Staff Veterinarian	USDA
	C. Thoen	Head, Mycobacteriology	USDA

COOPERATING UNITS (if any)
Veterinary Services Laboratories, Mycobacteriology Section, APHIS, USDA, Ames, Iowa 50010
Dept. of Veterinary Clinical Science, Univ. of Minnesota, St. Paul, Minnesota

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A comparison is being made of the immune response to PPD (purified protein derivative of tuberculin .6 to 6.5 mg per milliliter protein) and MT (mammalian tuberculin - USDA reference strength) using natural cases of primate tuberculosis. Results indicate that the hypersensitivity response to MT is linear, increasing with the amount of protein present. The hypersensitivity response to PPD is not linear, plateauing at approximately 2.0 mg per milliliter. The response was consistently of greater intensity to MT than to PPD, when equivalent strengths above .6 mg per milliliter of protein were used. MT appears to be the better product for diagnosing tuberculosis in rhesus monkeys.

Objective: Intradermal tuberculin testing in nonhuman primates is done primarily with commercially prepared USDA mammalian tuberculin (MT). This study compares the efficacy of Mycobacterium bovis purified protein derivative (PPD) with MT. Clinical pathology and immunologic parameters of primate tuberculosis are also being studied.

Methods Employed: Comparisons of MT and PPD are being made using equivalent concentrations, calculated according to the amount of protein in each product. The only exception is with eyelid intradermal testing, which compares various concentrations of PPD to full-strength mammalian tuberculin (FSMT). Test animals are selected from natural reactors during the quarantine period. Reactors are caged with healthy monkeys which are then tested at weekly intervals for conversion.

Major Findings: The FSMT (2.94 mg per milliliter) stimulated a greater reaction than MT diluted one part to ten. The responses to increasing concentrations of MT (0.6 mg to 2.94 mg) progressed in a linear manner. This linear progression was not observed with PPD. The reaction to PPD at 0.6 mg per milliliter was equivalent to, or greater than, to MT at that concentration. As PPD concentrations increased, the reaction intensity plateaued near 2 mg per milliliter and increased very little with concentrations up to 6.5 mg per milliliter, never reaching the intensity of FSMT. Both positive or suspect reactions to MT were elicited up to three weeks before those to PPD.

The results of lymphocyte transformation testing have not been completely analyzed. However, preliminary information indicates that the tuberculin testing interferes with lymphocyte stimulation. Whether this is dose related is uncertain. It will be studied further.

The findings to date indicate the erythrocyte sedimentation rate increases in all reactors, up to 22 mm per hour in one case. Other clinical pathologic parameters are being studied.

Significance: The study will permit evaluation of the most effective product for detection of tuberculosis in naturally exposed nonhuman primates.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00015-03 VR

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Defining the Nude Mouse Model

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	R.A. Whitney, Jr.	Chief	VRB DRS
OTHER:	C.T.Hansen	Geneticist	VRB DRS
	J.R. Ganaway	Veterinary Microbiologist	VRB DRS
	A.M. Allen	Chief, CPS	VRB DRS
	C.K. Hsu	Ft. Detrick, Maryland	FCRC
	H.J. Alter	Blood Bank	CC
	P. Holland	Blood Bank	CC
	R. Purcell		LID NIAID

COOPERATING UNITS (if any)
Laboratory of Infectious Diseases, NIAID
Blood Bank, Clinical Center
Dept. Laboratory Animal Medicine, Johns Hopkins U., Baltimore, Maryland
Frederick Cancer Research Center, Ft, Detrick, Maryland

LAB/BRANCH
Veterinary Resources Branch

SECTION
N/A

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0	0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A congenic strain of mouse crossed with CBA inbred will be used to again attempt to identify an animal model for human hepatitis A and B. This congenic strain CBA/nude will lack the thymus and T system of the nude and also lack some elements of the B immune system inherent in the CBA mouse.

Project has been suspended while awaiting production of congenic CBA/nude mouse.

PHS-6040
(Rev. 10-76)

PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00016-02VR

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Characterization of a New Viral Disease of Rabbits

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	J. D. Small	Animal Disease Investigator	SAS VRB DRS
OTHER:	R. A. Squire		Johns Hopkins University
	L. Aurelian	Virologist	Johns Hopkins University
	J. D. Strandberg	Pathologist	Johns Hopkins University

COOPERATING UNITS (if any)
Johns Hopkins University School of Medicine, Baltimore, MD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Small Animal Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The goal of this project is to isolate and characterize the agent responsible for a disease recently detected in rabbits, describe the clinical course, define the lesions, study the mode of transmission, and define the host range. Work so far indicates that the agent is a virus, the target tissue is muscle, and the only known susceptible host is the rabbit.

Work has been suspended pending availability of space and technical support.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-RS-00017-02 VR

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Experimental Atherosclerosis in Miniature Swine

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. W. Mahley	Head, CAAMS	IR NHLBI
	D. L. Fry	Chief, EA	IR NHLBI
	R. L. Killens	Head, CMU, VMSS	VRB DRS
	D. K. Johnson	Chief, VMSS	VRB DRS
	J. J. Knapka	Nutritionist, SAS	VRB DRS

COOPERATING UNITS (if any)
Laboratory of Experimental Atherosclerosis, NHLBI
Small Animal Section, VRB, DRS

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.0	2.0	2.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

To determine the effects of different kinds of dietary fats, with and without cholesterol, on the pathogenesis of atherosclerosis using miniature swine as an animal model for human disease. Experimental atherosclerosis in miniature swine provides a model system for studying the interrelationships of dietary and biochemical factors germane to the basic causes and mechanism of atherosclerosis.

PHS-6040
(Rev. 10-76)

Objectives: To determine the effects of different kinds of dietary fats, with and without cholesterol, on the pathogenesis of atherosclerosis.

Methods Employed: Fifty miniature swine of uniform age and size and equal sex distribution were obtained. After baseline blood chemistry studies, the animals were divided into groups receiving the following supplements to a defined swine diet: tallow, tallow with 1.5 percent cholesterol, tallow with 1.5 percent cholesterol plus 0.75 percent taurocholic acid; lard, lard with 1.5 percent cholesterol, lard with 1.5 percent cholesterol plus 0.75 percent taurocholic acid; cottonseed oil, cottonseed oil with 1.5 percent cholesterol. The swine were kept on the diet for six months. Blood chemistry was studied and animal weights determined weekly. Monthly serum samples were collected for isolation and measurement of specific lipoproteins.

Major Findings: Atherosclerosis was induced in swine fed the cholesterol diets. The degree and extent of the disease correlated with the level of total serum cholesterol. Significant findings were (1) thrombosis of the following arteries: basilar, cerebral, anterior descending coronary, and posterior descending coronary and (2) atherosclerosis with midrange serum cholesterol levels. In both distribution and appearance, the lesions resembled the disease in humans.

Significance: Detailed investigation of induced atherosclerosis in animal models such as miniature swine is needed to explore the underlying causes and progression of the disease. Atherosclerosis is a major disease of human beings, a leading cause of death, and a debilitating condition affecting all ages. The ability to produce the lesions in a reliable, reproducible manner permits evaluation of a variety of parameters.

Proposed Course: Study is completed and data is being analyzed for publication.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-RS-00018-03 VR

PERIOD COVERED

October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

The Pathogenesis of Chondrodysplasia in the Alaskan Malamute

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. M. Young	Acting Head, PS	LT NCI
	R. L. Killens	Head, CMU, VMSS	VRB DRS
	J. M. Ward	Veterinary Pathologist	LT NCI
	D. Prieur	Pathologist	LT NCI
	A. Guarino	Head, Toxicology	LT NCI

COOPERATING UNITS (if any)

Laboratory of Toxicology, National Cancer Institute

LAB/BRANCH

Veterinary Resources Branch

SECTION

Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION

DRS, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The Alaskan malamute has naturally occurring chondrodysplasia, an inborn error of metabolism that appears as a recessive trait with varying degrees of expression. The animal serves as a useful model for studying the pathogenesis of chondrodysplasia. Observation of growth patterns in puppies is especially useful. Studies of biochemical, histochemical, and morphological changes serve to define the disease in human beings. They may also elucidate mechanisms of pathogenic processes that occur with neoplasms of the skeletal system.

PHS-6040
(Rev. 10-76)

Objectives: To elucidate the pathogenesis of chondrodysplasia in the Alaskan malamute and compare these findings with those reported in man to determine if the skeletal disorder in the malamutes is a good model for chondrodysplasic dwarfism in man.

Methods Employed: A colony of ten Alaskan malamutes has been acquired. The dogs are mated and all offspring are radiographed at established intervals to detect early change and growth patterns indicative of chondrodysplasia. Currently, the main emphasis is on repeated breeding and evaluation of bitches and studs to obtain an increased number of puppies with the defect. Also, another colony of malamutes is being established to permit collection of additional baseline data.

Major Findings: The conception rates were very low during the year due to immature studs. A method of artificial insemination was implemented to induce pregnancy and to increase the number of pregnancies.

Significance: Cellular changes in cartilage and bone that accompany chondrodysplasia can be studied in the Alaskan malamute. Identification of morphological and biochemical alterations in animals with the disease elucidate cellular defects that occur with other diseases that affect bone and cartilage such as osteosarcoma.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 RS 00019-02 VR

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Aging Studies on HSR, HSR-Stroke Prone, and WKY Rats

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. L. Clarke	Veterinary Pathologist	CPS VRB DRS
OTHER:	S. Potkay	Chief, SAS	SAS VRB DRS
	C. T. Hansen	Geneticist	SAS VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.7	0.2	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective is to determine the nature and incidence of pathologic lesions that develop throughout the lifespan of HSR, HSR-stroke prone, and WKY rats. In each strain, 100 animals of both sexes will be selected for long-term holding. Some subjects will be killed at the following ages: 2 months, 8 months, 12 months, 15 months, 18 months, 21 months, and 28 months. Tissues will be studied by light microscopic methods, and if indicated, electron microscopic techniques. These strains have great potential as animal models for the study of cerebrovascular and hypertensive disease in human beings. Their value depends on accurate pathological description and documentation. In each strain, 100 animals of both sexes will be selected for long-term holding.

PHS-6040
(Rev. 10-76)

Objectives: To determine the nature and incidence of pathologic lesions that develop throughout the lifespan of HSR, HSR-stroke prone, and WKY rats. HSR rats are reported to be hypertensive. +140 mm Hg, but a pathologic study of the strain apparently has not been made. The HSR-stroke prone rat is reported to spontaneously develop cerebral infarcts, although documentation is sketchy. The WKY is the parent strain of the HSR and HSR-stroke prone rat and will be studied as a control.

Methods Employed: One hundred animals of each sex/strain will be selected for long-term holding. Some subjects will be killed at the following ages: 2 months, 8 months, 12 months, 15 months, 18 months, 21 months, 24 months, and 28 months. Tissues will be studied by light microscopic methods, and if indicated, electron microscopic techniques.

Significance: These strains have great potential as animal models for the study of cerebrovascular and hypertensive disease in humans. Their value depends on accurate pathological description and documentation and will have been established if correlation between the disease in the animals and human beings is good.

Proposed Course: Continuation. To date the animals have not been received.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-RS-00020-02 VR

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)
Intrautero Injection of Herpes saimiri and Epstein-Barr Virus in Pregnant Guinea Pigs

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	John W. Pearson	Head, VIS	LRTV NCI
	John D. Bacher	Head, SU, VMSS	VRB DRS

COOPERATING UNITS (if any)
C. Lingeman, TPB, NCI
J. Hunter, BGY, NCI
D. Twardzik, VO, NCI

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.3	.2	.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

All serum samples from 12 guinea pigs infected as weanlings via different routes of inoculation contained Viral Capsul Antigen (VCA) serum antibodies to Epstein Barr Virus (EBV) with titers ranging from 1:10 to 1:40 over a period of one year. No Early Antigen (EA) serum antibodies have been detected during this period. Fifteen animals inoculated intrautero or in the bone marrow with EBV have shown VCA serum antibodies (1:20 to 1:80) and, more important, nine revealed EA antibody to EBV, with titers ranging from 1:10 to 1:80 as judged by indirect immunofluorescence. Sera obtained from four of seven animals injected intrautero with Herpes saimiri (HVS) had antibodies of both VCA (1:20 to 1:80) and EA (1:10 to 1:20).

Objectives: The aim of this project is to study two primate oncogenic viruses, Epstein-Barr (EBV) and Herpes saimiri (HVS), with regard to infectivity and their transforming potential in vivo in guinea pigs and in various populations of guinea pig cells. In vitro techniques have been employed to follow vial infection based on antibody responses in guinea pigs inoculated with EBV or HVS.

Methods Employed:

1. Inoculation of fetal guinea pigs (20 to 40 days gestation) with EBV and HSV.

2. Inoculation of the same guinea pigs after birth with EBV and HSV.

3. Inoculation into the bone marrow of newborn guinea pigs.

4. Treatment of guinea pigs with guinea pig antithymus serum or drug suppressive therapy before inoculation of animals with either EBV or HVS.

5. Use of indirect immunofluorescence to monitor guinea pigs infected with EBV and HVS for humoral antibodies against associated antigens.

Major Findings: Eight guinea pigs injected intrautero with EBV followed by six weekly injections after birth have been under observation for three months. At two months, all animals exhibited Viral Capsule Antigen (VCA) serum antibodies (1:20 to 1:80), and recently five of eight animals revealed Early Antigen (EA) serum antibodies, with titers ranging from 1:10 to 1:80. So far, peripheral blood smears are normal. After inoculation of EBV ($10^{5.5}$ TU) into the bone marrow of newborn guinea pigs, all animals have serum antibodies to VCA, with titers ranging from 1:40 to greater than or equal to 1:80 as well as antibody to the EA antigen (1:20). These animals have been studied only six weeks and are being closely observed for signs of neoplasia.

Approximately three months ago, studies were undertaken to attempt to infect guinea pigs with HVS. Seven animals were injected intrautero with approximately $10^{5.0}$ $TCID/_{50's}$, followed by six weekly injections of virus beginning after birth. Two weeks after the last injection of virus, sera samples were taken and checked for serum antibodies against HVS via indirect immunofluorescence. Four of the guinea pigs exhibited VCA serum antibodies (1:20 to 1:80) when tested against owl monkey kidney cells infected with HVS. Three of the four animals positive for VCA antibody have exhibited EA serum antibody titers ranging from 1:10 to 1:20. Peripheral blood smears obtained from these three animals have remained normal. Because of the presence of EA antibody and subsequent occurrence of lymphomas in the primate model, the animals are being closely monitored for physical signs of neoplasia. Another four guinea pigs with HVS injected into the bone marrow at birth have all shown VCA antibody with titers ranging from 1:20 to 1:80. One of the four infected pigs has shown an EA titer of 1:10. Again, all peripheral blood smears have remained normal.

Significance: The long-term goal of this project is to develop a guinea pig model to study EBV, a virus implicated in human cancer, and HVS, a virus known to transform human cells in vitro. Such a model system could provide evidence of the involvement of these two herpes viruses in the pathogenesis of neoplasia and serve as a definitive model for investigating measures for prevention and treatment of cancer in human beings.

Proposed Course: The previously inoculated guinea pigs will be observed for the development of neoplasia. In addition, newborn guinea pigs immunosuppressed by removal of the cervical thymus will be inoculated with EBV and HVS.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-RS-00022-02 VR

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Skeletal Age Development in Macaca mulatta

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. Michejda	Comparative Anatomist, VMSS	VRB DRS
	W. Watson	Head, PRU, VMSS	VRB DRS
	R. L. Killens	Head, CMU, VMSS	VRB DRS
	J. D. Bacher	Head, SU, VMSS	VRB DRS
	N. R. Hayes	Deputy Chief, VMSS	VRB DRS
	D. K. Johnson	Chief, VMSS	VRB DRS

COOPERATING UNITS (if any)

N

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The most widely used methods (dental age, body weight) for age estimation in nonhuman primates are inadequate. More precise standards and age indicators are needed and can be obtained by measuring skeletal age, which has proven to be the the best criterion for assessment of chronological age. Our longitudinal radiographic studies will provide information on the development and bone maturation of the hand and wrist in Macaca mulatta monkeys. The data will cover the entire period of appendicular bone maturation, from 120 days of gestation (the onset of carpal center ossification) to adulthood (over five years). To obtain the fetal data, a novel surgical technique of multiple uterotomies was developed. Serial radiographic data are obtained at three uterotomies and after delivery. The pre- and postnatal age indicators will be prepared for publication as an atlas, which should make the data readily usable in many studies where the precise age of the experimental animal is required.

PHS-6040
(Rev. 10-76)

Objectives: To provide information on bone development and maturation of the hand and wrist in the rhesus monkey, Macaca mulatta. This information will be used for publication as an atlas and will serve as a comparison with human bone maturation.

Methods Employed: Longitudinal radiographic study of ossification centers in the hand and wrist of Macaca mulatta is being carried out in two age groups (30 animals each) to assess skeletal age. The first group was initially examined at 120 days of gestation, corresponding to the skeletal maturation of human newborns, and studies of the second group were started at 127 days of gestation. In the first group, uterotomies were performed and radiographic data were obtained every two weeks at 120, 134, 148, and 162 days of gestation. The last data were usually taken on neonates. In similar fashion, the second group provided data on alternative weeks at 127, 141, 155 days of gestation. The need for the two groups was necessitated by the surgical procedure and the rapid rate of growth changes, particularly in the ossification centers of the wrist, during the second trimester of fetal life. The pregnant animals would not have tolerated weekly surgery, but staggering of the two groups provided the necessary radiographic data on a weekly basis. During the uterotomies, the left hand of the fetus was temporarily removed from the uterus and radiographed. The uniform dorsopalmar projection was applied at a constant 40-cm tube-to-target distance. X-ray cassettes with intensifying Du Pont screens were used to reduce exposure time to a minimum (1/30 sec, 40 KV, 30 mA). Each radiograph was analyzed to assess onset and status of the ossification centers in the wrist and hand. The prenatal data will be incorporated with existing logitudinal postnatal data. Complete information about all stages of bone maturation and development in the hand and wrist of M. mulatta will be evaluated in five age groups: prenatal, neonatal, infant, juvenile, and adult.

Major Findings: Our longitudinal radiographic studies have shown characteristic growth patterns of carpal ossification centers on a weekly basis. No radiographic signs of carpal ossification centers were observed before 120 days of gestation. Between 120 to 127 days of gestation, the onset of ossification of radial epiphyses was observed. The ossification of one carpal bone per week was found between 127 and 141 days of gestation. After that period of relatively slow and regular carpal development, rapid ossification processes and radiographic appearance of two to three carpal bones per week were noted. In newborns six to seven carpal ossification centers were observed. Old World monkeys at maturity have nine carpal bones. Thus, six to seven of these centers are ossifying in prenatal stage. During the course of this study, a high rate (27 percent) of breech presentation was observed. The rotation of the fetus in utero, routinely performed in the second year of the study, had greatly decreased the rate of stillbirths and complications during delivery.

Significance: Assessment of bone maturation by use of roentgenograms of the extremities is the best method for determining age. It provides age estimates throughout the development period and allows detection of experimentally induced variations in the skeletal development.

Our data, obtained from normal fetuses, will be valuable for a variety of studies. The most important impact of it might be on experimental teratology and genetics, where rhesus monkeys of unknown age are widely used as models. It should constitute an important contribution to better understanding of prenatal development in Macaca mulatta. The data may also serve as a basis for comparison with human material in a variety of studies. Moreover, the success of the serial uterotomies may provide new possibilities for prenatal treatment of the human fetus, as for blood disorders when prenatal transfusion is needed but existing methods are risky; for skeletal disorders when early surgical treatment may be of great value; and perhaps for many other conditions that might be corrected by a surgical procedure before birth.

Proposed Course: Continuation of the study to its completion and preparation of a radiographic atlas of skeletal development of the hand and wrist of the M. mulatta.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00024-02 VR

PERIOD COVERED
October 1, 1977, to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Anthelmintic Effect on Antibody Levels Following Primary and Secondary Immune Stimulation

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	M.L. Morin	Veterinarian	VRB DRS
OTHER:	G.D. Hodgen	Chief, Endocrinology Section	NICHHD
	L.D. Stuart	Head, UU	VRB DRS
	F.J. Judge	Chief, ACS	VRB DRS

COOPERATING UNITS (if any)

Section on Endocrinology, Reproduction Research Branch, NICHHD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to determine if anthelmintics (thiobendazole or lavamisole hydrochloride) interfere with the normal immune response. Sheep receiving primary or secondary immune stimulation are being routinely wormed, and the circulating antibody responses determined. Preliminary results indicate that the anthelmintics do not affect antibody production.

PHS-6040
(Rev. 10-76)

Objectives: The objective is to determine if anthelmintics (thiobendazole and levamisole hydrochloride) interfere with normal immune response as measured by circulating antibody levels.

Methods Employed: Sheep receiving primary or secondary immune stimulation were routinely wormed, and the circulating antibody responses determined. Sheep were separated into three groups, one for each anthelmintic and one for saline control.

Major Findings: Preliminary information suggests that the drugs do not affect circulating antibody levels.

Significance: Preliminary findings indicate that routine worming practices do not affect the immunologic response of antibody-producing ruminants.

Proposed Course: Continuation.

NUMBER (Do NOT use this space)	HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00025-02 VR

COVERED
ber 1, 1977 to September 30, 1978

PROJECT (80 characters or less)

luation of a Purified Diet for Rodents

LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER ONAL PERSONNEL ENGAGED ON THE PROJECT

J. J. Knapka Nutritionist VRB, DRS

ING UNITS (if any)

CH
erinary Resources Branch

l1 Animal Section

E AND LOCATION
, NIH, Bethesda, MD 20014

NYEARS:	PROFESSIONAL:	OTHER:
1	.25	.075

PROPRIATE BOX(ES)

UMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

INORS ☐ (a2) INTERVIEWS

OF WORK (200 words or less - underline keywords)

eeding trial was conducted to compare the lifetime performance of inbred mice fed either a standard cereal-based diet or a purified diet mulated with 50 percent glucose. The performance of two generations evaluated for differences in growth, reproduction, and lesions associated n aging.

-76)

Objectives: To develop a purified diet for laboratory mice that will meet all the nutrient requirements of this species and test the effect of feeding a diet containing high levels of low-molecular weight carbohydrates to mice for their entire lifespan.

Methods Employed: This feeding trial was designed to compare the performance of two generations of mice fed the test-purified diet and a standard cereal-based diet. Criteria of evaluation included number of pregnancies, number of litters born and weaned, number of pups born and weaned, mortality, weight of offspring weaned, postweaning growth of offspring, total days of life, and the onset and distribution of lesions associated with aging. All data were analyzed by the appropriate statistical procedures.

Major Findings: A purified diet formulated with 50 percent glucose supported growth and reproduction in two generations of noninbred mice. Thirty-month-old mice fed the purified or a cereal-based diet their entire lives were examined at autopsy. Lesions associated with aging were essentially identical in both groups.

Significance: The study indicates that purified diets containing up to 50 percent glucose are safe for use in relatively long-term experiments involving mice.

Proposed Course: Discontinue.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00026-01 VR

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Subclinical Ascorbic Acid Deficiency in the Guinea Pig

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. L. Clarke	Veterinary Pathologist	CPS VRB DRS
OTHER:	A. M. Allen	Chief, CPS	CPS VRB DRS
	J. D. Small	Veterinarian	SAS VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.2	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

It is believed that subclinical scurvy is much more prevalent in guinea pig colonies than is generally appreciated and a major cause of animal losses. The study will create an awareness on the part of animal care personnel, clinicians, and pathologists as to the potential for subclinical scurvy to cause serious health problems in guinea pig colonies. Several episodes of this disease are presently being studied.

PHS-6040
(Rev. 10-76)

Objectives: To report the occurrence of subclinical scurvy as a cause of morbidity and mortality in guinea pig colonies.

Methods Employed: Collect naturally occurring cases of subclinical scurvy, that is, cases where ascorbic acid deficiency causes no overt gross lesions but considerable morbidity and mortality. Examine histologically all suspected animals and correlate findings with clinical history.

Significance: It is believed that subclinical scurvy is much more common in guinea pig colonies than is generally appreciated and that it is a major cause of animal losses. Our findings may increase awareness on the part of animal care personnel, clinicians, and pathologists as to the potential for subclinical scurvy to cause serious health problems in guinea pig colonies.

Proposed Course: Animals from several episodes have been collected and the material is being studied and prepared for publication.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00027-01 VR

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Linkage Analysis in the Laboratory Mouse

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	Harold A. Hoffman	Research Geneticist	CPS VRB DRS
OTHER:	Kitty P. Smith	Geneticist	CPS VRB DRS
	James S. Crowell, Jr.	Staff Fellow	CPS VRB DRS
	Alice H. Grier	Bio Lab Tech	CPS VRB DRS
	Anna V. Williams	Bio Lab Tech	CPS VRB DRS

COOPERATING UNITS (if any)
Cell Surface Antigen Laboratory, Memorial Sloan-Kettering Cancer Center
New York, NY

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.6	0.6	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This project is designed to identify and locate on the chromosomes of the laboratory mouse, genetic characteristics that can be used in a wide range of biomedical research. The areas of interest are: (1) characterization of the genetic trait by biomedical and immunochemical techniques; (2) chromosome mapping by standard genetic analyses; and (3) application of the genetic characteristics to explore new animal models useful in pathogenetic studies.

PHS-6040
(Rev. 10-76)

Objectives: To identify and locate on the chromosomes of the laboratory mouse genetic traits that can be used in a wide range of biomedical research areas.

Methods Employed: Analysis of isozymes by starch-gel electrophoresis; complement and serum proteins by agar-gel double diffusion (Ouchterlony Analysis) and immunoelectrophoresis; and cell surface alloantigens by cytotoxic methods.

Major Findings: The lymphocyte cell surface alloantigen Lyt-4 was located on chromosome 1. Lyt-4 is 3 centiMorgans (map units) from the enzyme dipeptidase (Dip-1). The gene order on chromosome 1 for the enzymes isocitrate dehydrogenase (Id-1) and depeptidase, and Ly-4 is: centromere---Id-1---Dip-1---Lyt-4.

Significance: By knowing the chromosomal location of the lymphocyte alloantigen Lyt-4, we are able to produce, by selective breeding, congenic lines for Lyt-4 with different genetic backgrounds. Lyt-4 congenic lines are essential for the production of monospecific alloantisera and serve as controls for Lyt-4 testing. Lyt-4 appears to have multiple functions; when its linkage relationship is known, congenic lines exhibiting a single immunologic characteristic can be made.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE
PROJECT NUMBER (Do NOT use this space)

HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NOTICE OF
INTRAMURAL RESEARCH PROJECT

Z01 RS 00028-01 VR

PERIOD COVERED
October 1, 1977, to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Histocompatibility Testing and Blood Grouping of Donor and Inbred Dogs

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	E.J. Baas	Head, CU	VRB DRS
OTHER:	T.L. Wolfle	Assistant Head, CU	VRB DRS
	F.J. Judge	Chief, ACS	VRB DRS
	R.W. Bull	Director, Research Immunohematology and Serology Lab	Michigan State University

COOPERATING UNITS (if any)

Department of Medicine, Michigan State University, East Lansing, Michigan

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.4	0.2	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Histocompatibility studies of blood donor and inbred dogs are being conducted to correlate chronic health problems with genetic and tissue antigen types. Results are being used to evaluate inbreeding progress, match breeding pairs, and possibly correlate histocompatibility to puppy mortality. The NIH canine blood donor colony is also being studied to more fully characterize canine tissue antigens and blood groups and delineate potential rare types.

Objective: The objective is to determine if histocompatibility and blood group types are important genetic factors in chronic health problems and can be used to guide the inbreeding of dogs.

Methods Employed: Leukocytes are being used in mixed lympocyte cultures, in determinations of cell antigens, and in lymphoblastogenesis tests. Erythrocytes are being used for blood grouping into eight or more major and minor Dog Erythrocyte Antigen types.

Significance: It has been documented in man that certain tissue types are more commonly associated with particular diseases. If this also occurs in diseases of the dog, animals with defined tissue types can be useful as models of human disease. The study will promote understanding of canine diseases, etiologic investigations of chronic health problems in dogs, and development of a more productive colony. The tissue and blood type data will help refine the inbred dogs so as to provide a better standardized model for research.

Proposed Course: Typing is now in progress. Results are being studied for breeding purposes and will be analyzed for correlations with chronic health problems.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00029-01 VR

PERIOD COVERED
October 1, 1977, to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Clinical Pathology Studies of Animal Health Conditions

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	E.J. Baas	Head, CU	VRB DRS
OTHER:	T.L. Wolfle	Assistant Head, CU	VRB DRS
	L.D. Stuart	Head, UU	VRB DRS
	M.L. Morin	Veterinarian, ACS	VRB DRS
	F.J. Judge	Chief, ACS	VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.3	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Studies are being conducted to define and characterize spontaneous clinical diseases occurring in the NIH ungulate herds and dog colonies. Preliminary clinical investigation has identified some disease problems. Hematological, bacteriological, and chemical tests are being made. The purposes of the investigations are to improve the quality of animals and animal products and characterize models of disease.

Objective: The objectives are to identify causes of diseases in NIH herds and colonies, help determine the pathogeneses, improve the quality of animals and animal products provided, and characterize models of disease.

Methods Employed: Several standard hematological, bacteriological, and chemical procedures are being employed at the Animal Center and through commercial laboratories. When an unusual technique or information is needed, assistance is enlisted from various institutions.

Major Findings: Johne's disease in goats has not been controlled through a culture test and slaughter method. Thus, a vaccination program has been instituted. The findings in the canine blood donor colony indicate that iron deficiency is important in some dogs but other deficiencies may play major roles in some chronic conditions.

Significance: It is necessary to identify the disease problems and control or eliminate them to provide improved animals and products for biomedical research. Complete characterization of some conditions may provide models of human conditions, or help illustrate the pathogenesis of animal conditions.

Proposed Course: Continuation of the present methods and incorporation of recent knowledge and methods to characterize chronic disease conditions.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00030-01 VR

PERIOD COVERED
March 1, 1978, to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Evaluation of Mycobacterium paratuberculosis Bacterin in the Goat

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	M.L. Morin	Veterinarian	VRB DRS
OTHER:	L.D. Stuart	Head, UU	VRB DRS
	R. Merkal	Research Veterinarian	NADL

COOPERATING UNITS (if any)

National Animal Disease Laboratory, Agriculture Research Services, Ames, Iowa

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.3	0.1	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study is designed to determine if a bacterin against Johne's disease will effect the incidence and age of onset of the disease in goats. One-half of the kid goats produced by Animal Center Section conventional does will be vaccinated at one month of age and observed for life.

Objectives: The objective is to determine if a bacterin against Johne's disease will affect the incidence and age of onset of the disease in goats.

Methods Employed: One-half of the kid goats produced by Animal Center Section conventional does will be vaccinated at one month of age with a whole-cell bacterin against Mycobacterium paratuberculosis. The other half (in most cases the twin) will be used as a control. The animals will be housed on contaminated pastures and will serve as usual in NIH programs. Animal cultures will be prepared to check for M. paratuberculosis. At the end of their usefulness or when they develop clinical Johne's disease, the goats will be necropsied and their Johne's disease status evaluated.

Major Findings: Findings will not be known until 1982.

Significance: With the use of a bacterin, it may be possible to prevent or delay the onset of Johne's disease in goats, as it is in cattle, thus enhancing the usefulness of goats in research.

Proposed Course: Continuation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00031-01 VR

PERIOD COVERED
February 28, 1978, to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Serum Hormone Levels in Feral Pregnant Rhesus Monkeys

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	M.L. Morin	Veterinarian	VRB DRS
OTHER:	D.M. Renguist	Head, PQU	VRB DRS
	G.D. Hodgen	Chief, ES	RRB NICHHD

COOPERATING UNITS (if any)

Endocrinology Section, RRB, NICHHD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.4	0.1	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☑ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to observe the changes in reproductive hormone levels in feral pregnant rhesus monkeys. These changes may explain the high incidence of abortion during the first month of quarantine. Also, information on hormone levels during gestation in feral rhesus monkeys will be compared with data obtained from laboratory-bred monkeys.

Objective: The objective is to observe the changes in reproductive hormone levels in feral pregnant rhesus monkeys.

Methods Employed: Adult female rhesus monkeys are examined for pregnancy when they arrive at our facilities. Pregnant animals are bled three times per week until the pregnancy is terminated by abortion or parturition. Estrogen and progesterone levels are measured in each serum sample.

Significance: The results may explain the high incidence of abortion during the first month of quarantine. The hormone levels of feral rhesus monkeys during gestation will be compared with similar data from laboratory-bred rhesus monkeys.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00032-01 VR

PERIOD COVERED
October 1, 1977, to September 30, 1978

TITLE OF PROJECT (80 characters or less)

The Effect of Dietary Crude Fiber on the Digestibility of Proteins, Lipids and Carbohydrates in Macaca mulatta

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	Dennis Barnard	Biological Laboratory Technician	VRB DRS
OTHER:	D.M. Renquist	Head, PQU	VRB DRS
	M.L. Morin	Veterinarian	VRB DRS
	J. Knapka	Nutritionist	VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.05	.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to determine the digestibility coefficients of lipids, proteins, and carbohydrates as affected by different levels of crude fiber in monkey diets. The study involves comparing a baked 7 percent crude fiber diet to baked and extruded standard 3 percent diets. The feces from twelve monkeys included in the study were collected and sent for laboratory analysis and determination of the digestibility coefficients.

Objective: The purpose of this study is to determine the digestibility coefficients of lipids, proteins, and carbohydrates as affected by different levels of crude fiber in nonhuman primate diets.

Methods Employed: Twelve rhesus monkeys acting as their own controls were fed experimental baked diets containing 3 percent and 7 percent crude fiber and a commercial extruded diet containing 3 percent crude fiber. Feed intake and fecal output were determined. Feces were analyzed to determine the digestibility coefficients.

Significance: This study follows up the Dietary Fiber Level Study (Z01 RS 00023-01 VR). It is important to understand what portions of the crude fiber (carbohydrate) are digestible and how varying the crude fiber level affects the digestibility of lipids, proteins, and other carbohydrates.

Proposed Course: Indefinite

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 RS 00033-01 VR

PERIOD COVERED
October 1, 1977, to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Application of Automatic Data Processing to Nonhuman Primate Colony Management

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	D.M. Renquist	Head, PQU	VRB DRS
OTHER:	Ralph Van Wey, Jr.	Management Analysis Officer	DRS
	Peter Basa	Computer Programmer	DCRT

COOPERATING UNITS (if any)

Divison of Computer Research and Technology

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.05	.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A system is being developed to computerize basic information obtained from nonhuman primates during the quarantine period. The system will be used to provide clinical histories, morbidity and mortality data, drug treatment effectiveness, and other information on either a colony or an individual basis. The system will ultimately be able to provide intramural research investigators with a complete clinical profile of monkeys at VRB.

Objectives: The objective is to computerize basic information about nonhuman primates during the quarantine period.

Methods Employed: Routine background information, daily clinical records, and diagnosis and treatment data are computer printed on forms. After issue of the animal, the form is key punched and the data stored for computer retrieval.

Major Findings: The project is in the developmental stage.

Significance: The system will be used to provide clinical histories, morbidity and mortality data, drug treatment effectiveness, and other information on either a colony or individual basis.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00034-01 VR

PERIOD COVERED
October 1, 1977, to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Reproductive Physiology of Selected Exotic Nonhuman Primates

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	D.M. Renquist	Head, PQU	VRB DRS
OTHER:	M.L. Morin	Veterinarian	VRB DRS
	Dennis Barnard	Biological Laboratory Tech.	VRB DRS
	Gary Hodgen	Chief, ES	NICHHD
	T.L. Wolfle	Assistant Head, CU	VRB DRS

COOPERATING UNITS (if any)

Endocrinology Section, RRB, NICHHD

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this study is to establish breeding systems for producing healthy Aotus, Saimiri, Saguinus, and Cercopithecus animals in a consistent manner for research investigators at NIH and other interested scientists. Basic reproductive parameters being studied include duration of gestation, male and female reproductive cycles, relationships of accessory sexual organs to sexual activity, male-female breeding ratios, reproductive hormone serum levels, puberty changes, infant development, and minimum reproductive age.

Objective: The objective of the study is to establish breeding systems for producing healthy exotic nonhuman primates.

Methods Employed: Data will be collected for the following parameters: duration of gestation, male and female reproductive cycles, relationships of accessory sexual organs to sexual activity, male to female breeding ratios, reproductive hormone serum levels, puberty changes, infant development, and minimum reproductive age.

Significance: This study will increase reproductive information to provide effective laboratory rearing of exotic nonhuman primates.

Proposed Course: Indefinite

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00035-01 VR

PERIOD COVERED
October 1, 1977, to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Developmental Parameters of the Foxhound

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI :	T.L. Wolfle	Assistant Head, CU	VRB DRS
OTHER:	E.J. Baas	Head, CU	VRB DRS
	F.J. Judge	Chief, ACS	VRB DRS

COOPERATING UNITS (if any)

None

LAB/BRANCH
Veterinary Resources Branch

SECTION
Animal Center Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.15	.05	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Accurate characterization of the foxhound is essential to development and definition of quality control programs for this laboratory animal. Blood pressure, growth rate, physiological and behavioral adaptation to environmental stress, birth weight and prediction of neonatal survivability are among the areas studied. Outdoor paddock housing constitutes one major environmental variable. Uniformity among animals, within and between studies, significantly enhances validity of research results and reduces costs by eliminating unsuitable animals and decreasing the need for repetition of studies.

Objective: The objective is to accurately characterize the foxhound as a model for biomedical research.

Methods Employed: Longitudinal studies of reproduction, growth, behavior, and disease processes are made. Blood pressure and hematological studies identify normal values and environmental characteristics that alter the normal or existing state.

Major Findings: Basic reproduction, growth, and hematologic parameters have been identified. The colony serves as a standard for English and American foxhounds.

Significance: The foxhound is becoming prominent as a research animal. It is essential to determine normal physiological values to provide high-quality dogs for research. This will ensure more uniform research results and increase efficiency by decreasing the need for duplication and eliminating unusable animals.

Proposed Course: Indefinite

PROJECT NUMBER (Do NOT use this space)	HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 00036-01 VR

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)
Genetic Profile of NIH Inbred Rat Strains

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	K. P. Smith	Geneticist	CPS VRB DRS
OTHER:	H. A. Hoffman	Research Geneticist	CPS VRB DRS
	C. T. Hansen	Geneticist	SAS VRB DRS

COOPERATING UNITS (if any)
Small Animal Section, VRB, DRS

LAB/BRANCH
Veterinary Resources Branch

SECTION
Comparative Pathology Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
8.0	5.0	3.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The objective of this project is to develop a genetic profile and a genetic linkage map for the 26 inbred rat strains maintained by VRB. The genetic profile will include determination of genetic differences and similarities among the strains for various parameters, including morphology, proteins, enzymes, and immunological responses. A genetic map that defines the linkage relationships among the various loci will be developed. The principle method employed is starch-gel electrophoresis for separation of proteins and enzymes. Special mating systems including production of F_1 hybrids and backcrosses will be necessary for genetic analysis of the linkage data.

PHS-6040
(Rev. 10-76)

Objectives : To develop a genetic profile and a genetic linkage map for the 26 inbred strains maintained by the VRB. The genetic profile will include determination of genetic differences and similarities among the strains for various parameters including morphology, proteins, enzymes, and immunological responses. A genetic map that defines the linkage relationships among the various loci will be developed.

Methods Employed: The principle method employed is starch-gel electrophoresis for the separation of proteins and enzymes. Special mating systems including production of F_1 hybrids and backcrosses will be necessary for the genetic analysis of the linkage data.

Major Findings: Analyses have been completed for two enzymes, esterase and malic enzyme, and for one protein blood hemoglobin for all 26 strains. Five different phenotypes were found for kidney esterase. Three of these have not been previously described in the literature. These five phenotypes are controlled by at least two different genetic loci. Malic enzyme showed no variation among the strains. Two hemoglobin phenotypes were found in the 26 strains; 62 percent of the strains were type "a" and 38 percent were type "b."

Significance: The genetic profiles will make it possible to monitor the inbred rat strains for their genetic integrity. It is of paramount importance that the genetic integrity of these strains be assured because they are used throughout the biomedical community. The genetic information obtained will also make the strains more valuable as animal models.

Proposed Course: Continuation

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01-RS-00037-01 VR

PERIOD COVERED
October 1, 1977 to September 30, 1978

TITLE OF PROJECT (80 characters or less)

Fetal Surgery in the Macaca mulatta

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M. Michejda	Expert Consultant, VMSS	VRB, DRS
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COOPERATING UNITS (if any)

Comparative Medicine Unit, VMSS
Primate Research Unit, VMSS

LAB/BRANCH
Veterinary Resources Branch

SECTION
Veterinary Medicine and Surgery Section

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, MD 20014

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.4	.2	.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Multiple uterotomies on pregnant rhesus monkeys are being done to expose the hand of fetuses ranging in age from 120 to 163 days of gestation. The surgical procedure is being performed to establish an atlas for estimating skeletal age of the rhesus monkey before birth.

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Objective: The aim of this project is to describe the surgical procedure used and to evaluate the effect of multiple uterotomies on pregnant rhesus monkeys.

Methods Employed:

Multiple uterotomies will be performed in sixty timed-pregnant rhesus monkeys on alternate weeks starting at 120 or 127 days gestation to expose the carpus of the fetal monkey. The mother is fasted eighteen hours prior to surgery. Ketamine hydrochloride, 10 mg per kilogram, and atropine, .05 mg per kilogram, are given intramuscularly fifteen minutes before surgery. Ten milligrams of isoxsuprine HCL (Vasodilan®) is given thirty minutes prior to surgery and immediately after surgery to relax the uterine musculature. If needed, thiamyl sodium (Surital) is given to facilitate intubation. Preoperative radiographs are taken to determine if the fetus is still alive and to provide details on fetal position. Anesthesia is maintained with nitrous oxide, oxygen, and one percent halothane. Assisted mechanical respiration is used to insure adequate fetal oxygenation. The monkey is prepared for aseptic surgery and a ventral midline incision is made. The uterus is palpated to determine the location of the placental attachment and an incision two to three centimeters is made through the uterus and amnion over the head of the fetus and outside the limits of the placental girdle. No attempt is made to save the amnionic fluid. The hand of the fetus is found in the uterus, carefully pulled out, and positioned on a cassette that has been placed in a plastic bag previously sterilized with ethylene oxide. As soon as the two anteroposterior radiographs are taken, the hand of the fetus is placed back in the uterus which is closed with three separate layers of suture.

Major Findings: While monkeys are anatomically similar to man, they abort more frequently, particularly after intrauterine surgery. At the beginning of the study, a relatively high incidence of abortions led to improvement of the standard surgical procedures and postoperative care. Oxygen flow rates were increased from one to two liters per minute, the use of heating lamps was prolonged (minimum 48 hours postoperative), and the administration of anti-abortive medication (Vasodilan 10 mg) became standard postoperative procedure.

Significance: Current antenatal surgical procedures (in man) are presently used chiefly for diagnostics. Those used most frequently are amniocentesis, amniography, fetography, fetal skin biopsy, and fetal blood transfusions. Fetal and maternal risks are high in antenatal surgery and further improvement of techniques is needed.

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